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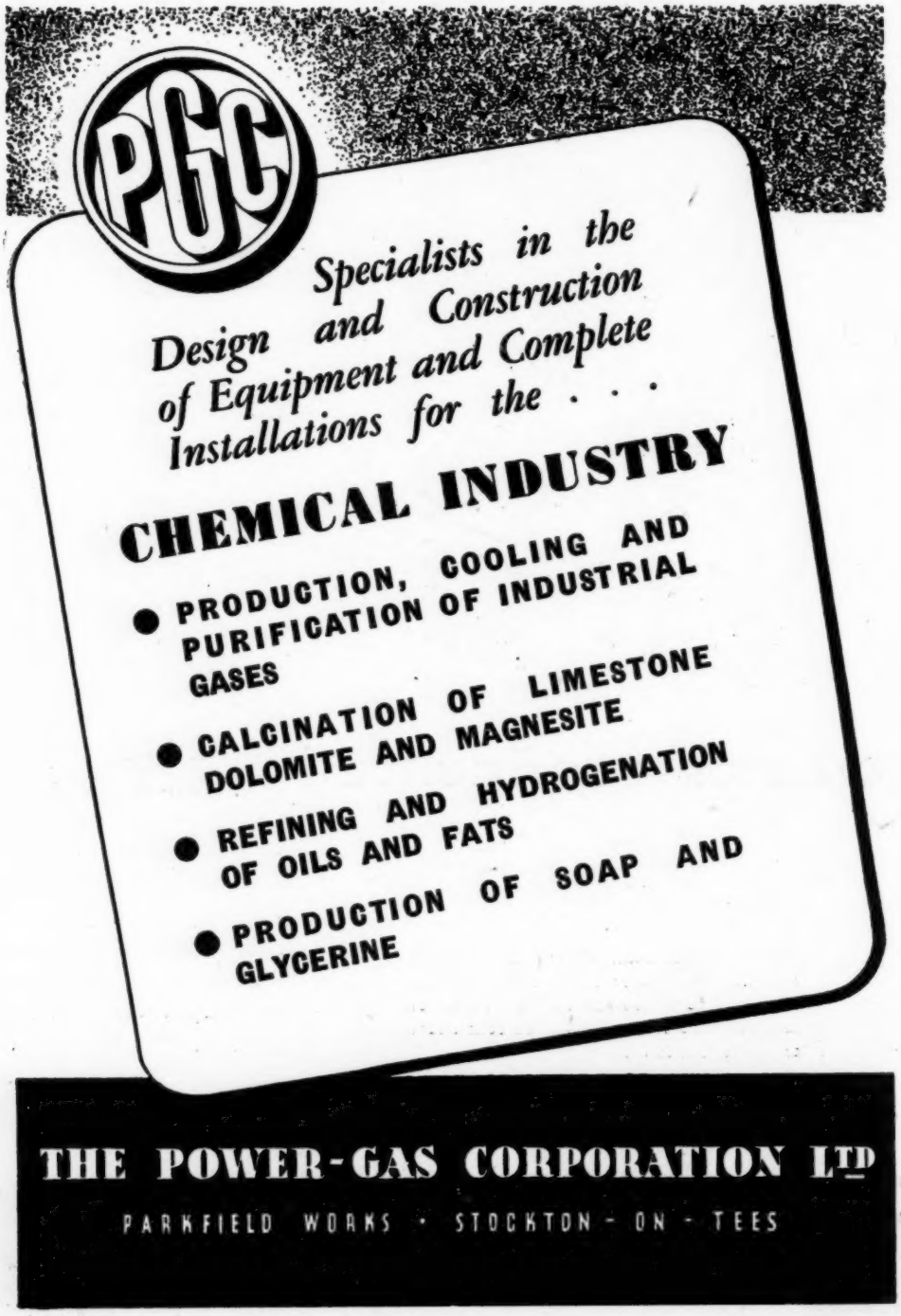
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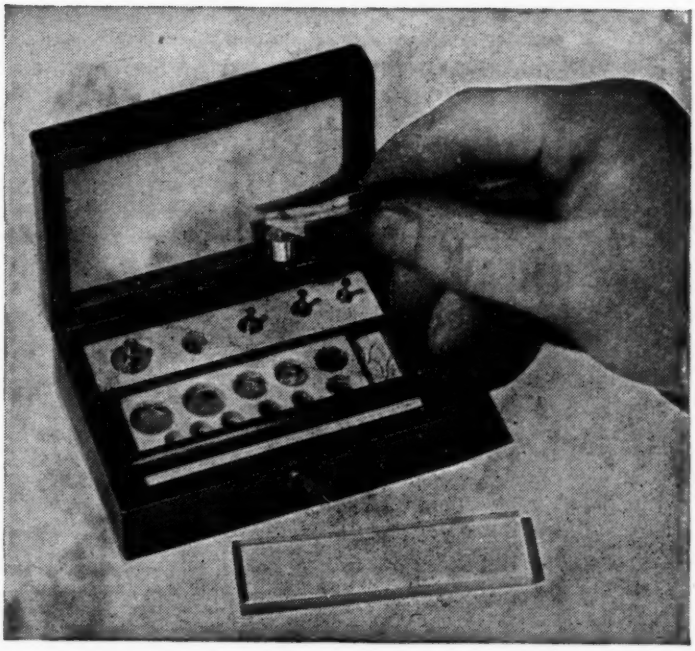

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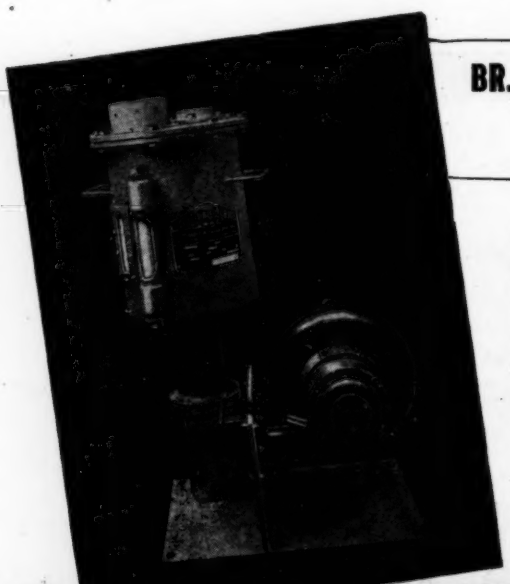

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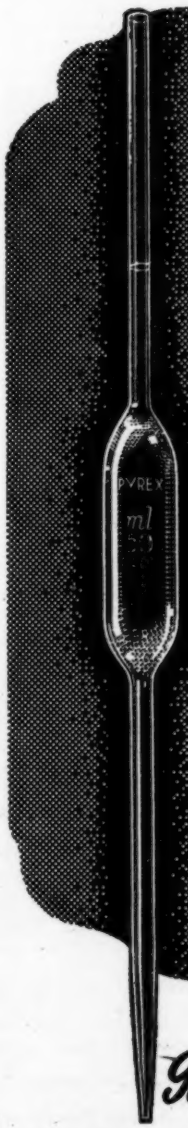

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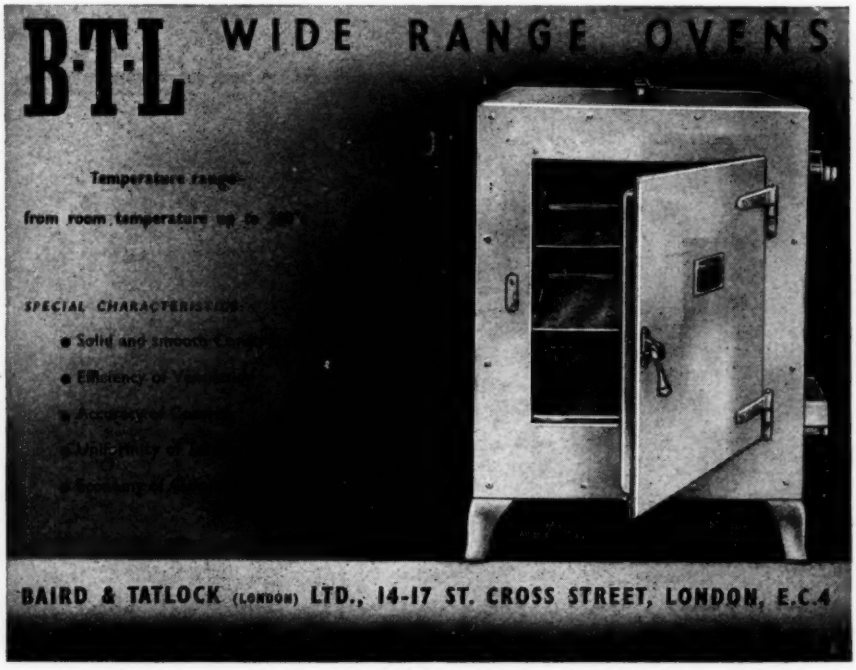

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phthalate in 84% yield, crystallised from benzene–light petroleum (b. p. 60—80°) in yellow prisms. m. p. 74—75° (Found : C, 54·7; H, 5·9. $C_{13}H_{15}O_4N_3$ requires C, 54·3; H, 5·7%).

Reaction with benzene. Dry hydrogen chloride and a solution of the triazen (20 g.) in benzene (250 c.c.) being used as described under the preparation of diphenyl (method i), a residue was obtained which on distillation in a high vacuum gave a yellow oil (13·4 g.), b. p. 130—150°/*ca.* 10^{-5} mm., which solidified when cold. Recrystallisation from light petroleum (b. p. 40—60°) gave methyl 4-phenylphthalate in white needles, m. p. 62—63°, both alone and on admixture with an authentic specimen (yield, 66%). Hydrolysis with aqueous sodium hydroxide gave 4-phenylphthalic acid, m. p. and mixed m. p. 193—194°.

Preparation of 4-Phenylphthalimide and of Methyl 4-Phenylphthalate by Means of the Gomberg Reaction (cf. Elks, Haworth, and Hey, *loc. cit.*).—4-Aminophthalimide (42 g.), suspended in a mixture of hydrochloric acid (*d* 1·16; 420 c.c.) and water (420 c.c.), was diazotised at 0—3° with aqueous sodium nitrite (21 g. in 63 c.c. of water). One half of the filtered diazonium solution was added to benzene (400 c.c.), vigorously stirred at 5—10°, and treated gradually with aqueous sodium hydroxide (90 g. in 450 c.c. of water), and the other half was added to the same volume of benzene and treated similarly with aqueous sodium acetate (285 g. of the hydrate in 650 c.c. of water). Stirring was continued for 48 hours, the reaction being allowed to proceed at room temperature after the first 3 hours. The benzene layers were then separated, washed with water, and distilled. The sodium hydroxide reaction yielded only a brown residue of high m. p., but the benzene layer from the sodium acetate reaction yielded a small residue of 4-phenylphthalimide, which after crystallisation from alcohol melted at 203—204° both alone and on admixture with the product prepared by Butterworth, Heilbron, Hey, and Wilkinson (*loc. cit.*) from 4-phenylphthalic anhydride and urea (Found : C, 75·1; H, 4·1. Calc. for $C_{14}H_9O_2N$: C, 75·3; H, 4·1%).

Methyl 4-aminophthalate (60 g.), dissolved in a mixture of hydrochloric acid (*d* 1·16; 115 c.c.) and water (25 c.c.), was diazotised at 0° with aqueous sodium nitrite (22 g. in 44 c.c of water). The filtered diazonium solution was divided equally, added to benzene, and treated with aqueous solutions of sodium hydroxide (22 g. in 70 c.c. of water) and of sodium acetate (65 g. of the hydrate in 180 c.c. of water) as in the previous example. When the reactions were complete, the benzene layers were separated, dried, and distilled. The residues were distilled in a high vacuum (*ca.* 10^{-5} mm.) at 130—150°. The colourless distillates solidified and on crystallisation from light petroleum (b. p. 40—60°) methyl 4-phenylphthalate separated in white needles, m. p. 62—63°, both alone and on admixture with an authentic specimen. The sodium hydroxide reaction gave 13·2 g. (yield, 34%), and the sodium acetate reaction 20·3 g. (yield, 52%).

This work was carried out under the auspices of the Advisory Research Council of the Chemical Society.

Imperial College of Science and Technology, London, S.W.7. [*Received, April, 29th,* 1943].

NOTES.

Some Ethers of 4-Chloro-2-nitro-3 : 5-dimethylphenol. By Brynmor Jones.

In Part X of the series " The Halogenation of Phenolic Ethers and Anilides " (J., 1941, 267) velocity coefficients for the chlorination of some ethers of 4-chloro-2-nitro-3 : 5-dimethylphenol were recorded. It is now found that one of these is incorrectly reported. The value $k = 0{\cdot}0728$, given in the last column of Table II, is for the hexyl ether and not for the benzyl ether : no measurements were made with the latter.

The following properties of the ethers inadvertently omitted from Part X, are now placed on record.

4-Chloro-2-nitro-3 : 5-dimethylphenol, m. p. 90°, prepared from 4-chloro-3 : 5-dimethylphenol by nitration with concentrated nitric acid in glacial acetic acid and purified by steam distillation and crystallisation from ligroin (b. p. 90—120°), was converted by standard methods into the following ethers. Each of these ethers was purified by crystallisation from glacial acetic acid and from ethyl alcohol; from the latter solvent they all crystallised in pale yellow, slender prisms : *methyl* ether, m. p. 166° (Found : C, 50·3; H, 4·7. $C_9H_{10}O_3NCl$ requires C, 50·1; H, 4·7%); *ethyl* ether, m. p. 107° (Found : C, 52·6; H, 5·3. $C_{10}H_{12}O_3NCl$ requires C, 52·3; H, 5·3%); n-*propyl* ether, m. p. 68° (Found : C, 54·3; H, 5·8. $C_{11}H_{14}O_3NCl$ requires C, 54·2; H, 5·8%); n-*hexyl* ether, m. p. 41° (Found : C, 59·4; H, 7·2. $C_{14}H_{20}O_3NCl$ requires C, 58·8; H, 7·1%); p-*bromobenzyl* ether, m. p. 105° (Found : C, 47·8; H, 3·3. $C_{15}H_{12}O_3NClBr$ requires C, 48·6; H, 3·5%). The *benzyl* ether, m. p. 105° (Found : C, 61·7; H, 4·9. $C_{15}H_{14}O_3NCl$ requires C, 61·8; H, 4·8%), was obtained by the nitration of 4-*chloro*-3 : 5-*dimethylphenyl benzyl ether*, m. p. 57° (Found : C, 72·7; H, 6·0. $C_{15}H_{15}OCl$ requires C, 73·0; H, 6·1%), in glacial acetic acid, 2—3 mols. of fuming nitric acid being used.—The University, Sheffield, 10. [*Received, April 29th,* 1943.]

The Polymerisation of Acetaldol. By L. N. Owen.

In connection with other work, it was necessary to determine the ease of polymerisation of aldol, and cryoscopic determinations in water and in dioxan showed that dimerisation of freshly distilled aldol is complete in a few hours, though, as the experimental figures show, the rate varies somewhat with different samples (see Table I). In these two solvents there was no alteration in the molecular weight of each sample over a period of several hours, from which it follows that further dimerisation is inhibited when the aldol is in solution. In one instance, when an aqueous solution of viscous aldol was kept for several weeks, there was a gradual fall in the molecular weight, in agreement with the observations of Späth, Lorenz, and Freund (*Ber.*, 1942, **75**, 1029), though the possible attainment of an equilibrium was not investigated.

In acetic acid, the observed molecular weight is independent of the age of the aldol and corresponds to a mixture of 20% monomer with 80% dimer, though in view of the abnormal values which are not uncommon in cryoscopic work these figures may not be a true indication of the existence of an equilibrium mixture. There can be no doubt, however, that this solvent, unlike water and dioxan, favours polymerisation, and this conclusion is supported by the observation that the addition of a small quantity of acetic acid to freshly distilled mobile aldol produces a rise in temperature, followed by an increase in viscosity which is more rapid than that observed during the normal polymerisation of aldol.

Experiments in benzene solution failed owing to the low solubility of paraldol in this solvent (approximately 0·2% at 10°). Nowak (*Monatsh.*, 1901, **22**, 1140) experienced the same difficulty, although Connolly (this vol., p. 42) has recorded figures for the molecular weight of paraldol determined by the cryoscopic method in benzene.

The addition to monomeric aldol of typical anti-oxidants failed to prevent polymerisation.

Table I.

Age of aldol (mins.)		3	5	15	20	45	60	120	240	1440	4320
% Dimer present (by weight) from *M* in	dioxan	—	46	42	76	106	—	—	106	106	103
	water	13	—	—	—	—	71	—	98	—	98
	acetic acid	—	80	—	—	—	79	79	81	80	82

Acetaldol was supplied by A. Boake, Roberts and Co., Ltd., in the form of a semi-solid polymer. By distillation under reduced pressure it was obtained as a mobile oil, b. p. 80°/16 mm. This gradually became viscous and after several hours crystallisation of the paraldol usually commenced.

Solubility of Crystalline Paraldol in Benzene.—The solid paraldol was separated from adhering oil, washed with ether, and dried in a vacuum. A small amount (50 mg.) dissolved readily in warm benzene (20 c.c.), but on cooling to 10° crystallisation began. After ½ hour at 10°, the feathery needles were collected and dried. Yield 12 mg., m. p. 88°. The solubility at 10° was therefore approximately 0·2%, and it was evident that for cryoscopic experiments in benzene the permissible concentration was so low that the results would be of little value.

Qualitative Tests on the Ease of Polymerisation of Aldol.—Freshly distilled aldol was treated in portions of 0·1 g. with about 1 mg. of each of the following substances: acetic acid, benzoic acid, quinol, pyrogallol, α-naphthol, β-naphthol, *p*-aminophenol. With acetic acid and benzoic acid there was a rise in temperature and marked increase in viscosity within 10 minutes. The other samples became viscous in about 1 hour, behaving in this respect in the same way as pure aldol.

Molecular-weight Determinations.—Hess and Frahm (*Ber.*, 1938, **71**, 2627), working with specially purified dioxan, found 4·83° for the cryoscopic constant. This figure was used for the present work.

The aldol was freshly distilled before each determination of molecular weight, a first fraction being rejected. A second fraction, of about 1 g., was then collected and kept at room temperature (18—21°) for the appropriate length of time. The amount required for the determination was then weighed out by difference from the receiver directly into the solvent in the cryoscopic apparatus. The figures given for the " age of aldol " refer to the time which elapsed between collection of the specimen and its addition to the solvent.

Data.—(a) *In dioxan.*

Age of aldol (mins.)	5	15	20	45	240	1440	4320
G. of aldol	0·185	0·083	0·129	0·197	0·134	0·231	0·161
G. of dioxan	11·0	11·1	11·0	11·0	11·1	11·0	11·0
$\Delta\theta$	0·71	0·325	0·40	0·46	0·31	0·54	0·39
M	114	111	142	188	188	188	181

(b) *In water.*

Age of aldol (mins.)	3	60	240	4320
G. of aldol	0·274	0·267	0·167	0·427
G. of water	10·6	10·6	10·5	10·6
$\Delta\theta$	0·51	0·34	0·17	0·43
M	94	136	172	173 *

* After 6 days at room temperature, this aqueous solution had $\Delta\theta = 0·59°$, whence $M = 126$; and after 26 days, $\Delta\theta = 0·69°$, $M = 109$.

(c) *In acetic acid.*

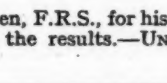
Age of aldol (mins.)	5	5	60	120	240	1440	4320
G. of aldol	0·119	0·122	0·150	0·147	0·103	0·118	0·255
G. of acetic acid	11·3	11·1	11·2	11·0	11·3	11·2	11·1
$\Delta\theta$	0·28	0·29	0·36	0·36	0·24	0·28	0·60
M	147 *	148 *	146	145	148	147	149

* In these two instances the freezing point of the solution did not attain a constant value until 20 minutes after the addition of the aldol, showing that polymerisation was taking place.

The author is indebted to Professor J. L. Simonsen, F.R.S., for his interest, and to Messrs. A. Boake, Roberts and Co., Ltd., for a grant and for permission to publish the results.—UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, June 9th*, 1943.]

Alkyl–Oxygen Fission in Sulphinic Esters. By MICHAEL P. BALFE, JOSEPH KENYON, and ANDRÁS L. TÁRNOKY.

THE structural similarity between the carboxyl and the sulphinyl group suggests that in sulphinic esters alkyl–oxygen fission may be expected to occur analogously to its occurrence in some carboxylic esters (J., 1942, 556, 605; *Nature*, 1941, **148**, 196):



Some recorded observations support this suggestion. The rearrangement of (−)-phenylmethylcarbinyl *dl*-*p*-toluene sulphinate to *dl*-*p*-tolyl-α-phenylethylsulphone (Arcus, Balfe, and Kenyon, J., 1938, 485) obviously involves alkyl–oxygen fission. (−)-Phenylmethylcarbinyl *dl*-*p*-toluenesulphinate on reaction with acetic acid gives the racemic acetate, and with ethyl alcohol gives the ethyl ether with extensive, though not complete, racemisation (Kenyon, Phillips, and Taylor, J., 1933, 173).

Ethyl (+)-β-*dl*-*p*-toluenesulphinoxy-β-phenylpropionate with formic acid gives a half racemised formate, and with ethyl alcohol a half racemised ethyl ether (Kenyon, Phillips, and Shutt, J., 1935, 1663). On the other hand, the acetate formed by interaction of (−)-β-octyl *dl*-*p*-toluenesulphinate and acetic acid shows no racemisation or change of configuration (Phillips, J., 1925, **127**, 2552) and (+)-β-butyl *dl*-*p*-toluenesulphinate (Kenyon, Phillips, and Pittman, J., 1935, 1072) reacts, without racemisation or change of configuration, with formic acid, yielding (+)-β-butyl alcohol, and with acetic acid, yielding a mixture of the alcohol and its acetate.

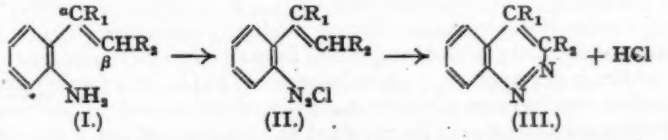
Thus, the racemising alkyl–oxygen fission reaction is promoted by the electron-release of an aromatic substituent in the alkyl group. The case of ethyl (+)-β-*dl*-*p*-toluenesulphinoxy-β-phenylpropionate is, however, somewhat complicated; in the two examples quoted above, the optically active portion of the ethyl ether is formed with inversion of configuration and that of the formate with retention of configuration; in addition (Kenyon, Phillips, and Shutt, *loc. cit.*), the sulphinate reacts with acetic acid with retention of configuration and absence of racemisation (acyl–oxygen fission).—BATTERSEA POLYTECHNIC, LONDON, S.W. 11. [*Received, May 17th*, 1943.]

120. *Cinnolines. Part II. The Influence of Substituents on the Widman–Stoermer and the Pschorr Reaction.*

By James C. E. Simpson.

A review of the published evidence respecting cyclisation of diazotised *o*-amino-ethylenes of type (I) leads to the conclusion that the Widman–Stoermer cinnoline synthesis (I ⟶ III) is inhibited when R_1 = H or CO_2H and R_2 = aryl or another negative group such as CO_2H, CO_2Et, or CN. In contrast to these results, it has now been found that the *amino-ethylenes* (IX), (X), and (XI) on diazotisation cyclise with extreme readiness to 3 : 4-*diphenyl*-, 4-*phenyl*-3-*benzyl*-, and 4-*phenyl*-3-(1′-*naphthyl*)-*cinnoline* respectively. In the last reaction 2-*phenylchrysene* (XIII) is formed in small quantity by a concomitant Pschorr reaction, and under suitable conditions the amount can be considerably increased to the exclusion of cinnoline-formation. The attachment of a phenyl group to the α-carbon atom of the amino-ethylene is evidently a dominant factor favouring cinnoline-formation; this is particularly well illustrated in the case of (IX), both geometrical forms of which yield the cinnoline and no 9-phenylphenanthrene, whereas the *cis*- and the *trans*-form of 2-aminostilbene furnish, respectively, phenanthrene and *trans*-stilbene or *trans*-2-hydroxystilbene on diazotisation.

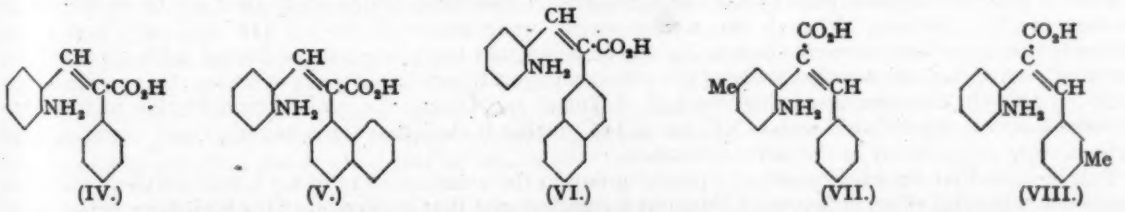
The synthesis of cinnolines by the Widman–Stoermer reaction (Widman, *Ber.*, 1884, **17**, 722; Stoermer and Fincke, *ibid.*, 1909, **42**, 3115; Stoermer and Gaus, *ibid.*, 1912, **45**, 3104; Simpson and Stephenson, J., 1942, 353) involves the diazotisation of *o*-aminoaryl-ethylenes, followed by cyclisation, which usually occurs spontaneously (I ⟶ II ⟶ III):



(I.) (II.) (III.)

Little attention has been paid to the question of the influence exerted by substituents R_1 and R_2 on the ease of formation of the hetero-ring, although Stoermer and Gaus (*loc. cit.*) have deduced, from the fact that *o*-aminocinnamic acid does not yield a cinnoline, that a negative group (R_2) on the β-ethylenic carbon atom of the amino-ethylene inhibits the cyclisation. These authors also state that an increase in the negative character of the substituent (R_1) on the α-carbon atom of the amino-ethylene facilitates cinnoline-formation, but no evidence in support of this assertion has been presented.

There is in fact considerable published evidence to the effect that, when R_2 is negative, particularly aryl, compounds of type (I) do not yield cinnolines on diazotisation. A striking illustration of this point is to be found in certain applications of the Pschorr reaction. In examples such as the synthesis of phenanthrene-9-carboxylic acid from (IV) (Pschorr, *Ber.*, 1896, **29**, 496), of chrysene-1-carboxylic acid from (V) (Weitzenböck and Lieb, *Monatsh.*, 1912, **33**, 549), and of 3 : 4-benzophenanthrene-10-carboxylic acid, mixed with 1 : 2-benzanthracene-4-carboxylic acid, from (VI) (Mayer and Oppenheimer, *Ber.*, 1918, **51**, 510; Cook, J., 1931, 2524), cinnoline-formation is clearly out of the question, owing to the absence of the necessary hydrogen on the β-carbon atom. In compounds (VII) and (VIII), on the other hand, this hydrogen atom is available, and cyclisation to cinnoline derivatives is thus an *a priori* possibility. Mayer and Balle (*Annalen*, 1914, **403**, 167), however, have shown that diazotisation of (VII) and (VIII) leads respectively to 2-methylphenanthrene-10-carboxylic acid and a mixture of 2- and 4-methylphenanthrene-9-carboxylic acids. The non-formation of cinnolines from (VII) and (VIII) is thus apparently attributable either to the aryl residue on the β-carbon atom or to the carboxyl on the α-carbon atom, or to both of these factors.



(IV.) (V.) (VI.) (VII.) (VIII.)

Now 2-aminostilbenes in which both the α- and the β-ethylenic carbon atom carry hydrogen atoms also show a characteristic behaviour on diazotisation. Although the reaction has not been studied with every known 2-aminostilbene of this type, it has been shown in several instances that the diazonium salt decomposes on warming with production of benzaldehyde. Examples of this are the diazotisations of 2-amino- and 4-nitro-2-amino-stilbene (Sachs and Hilpert, *Ber.*, 1906, **39**, 899), and of 2-amino-4-cyanostilbene (Ullmann and Gschwind, *ibid.*, 1908, **41**, 2291), although the second compound behaves normally in that its diazonium salt yields a diazoamino-compound with aniline. The failure of these stilbenes to undergo the expected Pschorr cyclisation is due to the fact that they are *trans*-derivatives, for Ruggli and Staub (*Helv. Chim. Acta*, 1937, **20**, 37) and Taylor and Hobson (J., 1936, 181) have shown that *cis*-2-aminostilbene furnishes phenanthrene after diazotisation, the former authors isolating the hydrocarbon in yields as high as 80%. More recently, an 18% yield of phenanthrene has been obtained from tetrazotised *cis*-2 : 4′-diaminostilbene by Ruggli and Dinger

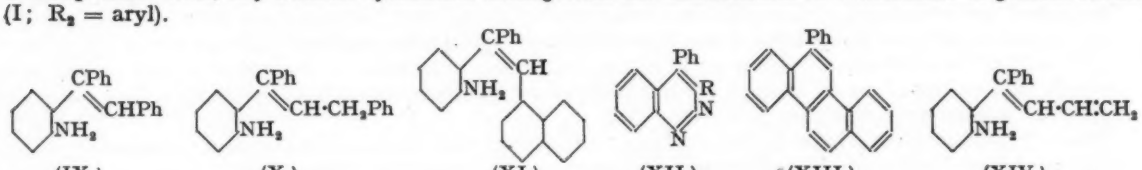
(*Helv. Chim. Acta*, 1941, **24**, 173), whereas the *trans*-diamine gave stilbene (13%) as the sole isolable product. Similarly, a re-investigation of the diazotisation of *trans*-2-aminostilbene by Ruggli and Staub (*loc. cit.*) showed that, according to the conditions used, *trans*-stilbene (62%) or *trans*-2-hydroxystilbene and a little benzaldehyde are produced.

The essential point which emerges from these considerations is that *cis*-2-aminostilbenes, in which both the α- and the β-carbon atom carry hydrogen atoms, behave normally in the Pschorr reaction, but that neither they nor their *trans*-isomers undergo cinnoline cyclisation.

A third category of substances of type (I) in which R_2 is negative comprises *o*-aminocinnamic acid and its simple derivatives. Here again, no instance of cinnoline-formation has been recorded. Diazotisation of the free acid leads to the formation of coumarin, coumaric acid, or cinnamic acid according to the experimental conditions (Fischer, *Ber.*, 1881, **14**, 479; Stoermer and Heymann, *ibid.*, 1912, **45**, 3099); *o*-aminocinnamic ester furnishes the *o*-cyano-ester in the Sandmeyer reaction (Komppa, Öf. Finska Vetenskaps-Societetens Förhandlingar, **36**, 121; Linstead and Noble, J., 1937, 936); and *o*-aminocinnamonitrile gives an inconclusive result (production of an alkali-soluble dark oil; Pschorr, *Ber.*, 1898, **31**, 1296).

The available data thus lead to the conclusion that the formation of cinnolines from compounds of type (I) does not occur in cases where R_2 is aryl or another negative group and R_1 is either hydrogen or carboxyl.

In this paper are recorded the results of diazotisation of some new *o*-amino-ethylenes of type (I) in which R_1 = phenyl. The *compounds* (IX), (X), and (XI) were prepared by the Grignard reaction between *o*-aminobenzophenone and the appropriate aryl halide, followed by dehydration of the resultant dl-*carbinols*. Diazotisation of (IX) and (X) yielded **3 : 4-*diphenylcinnoline*** (XII; R = Ph) and **4-*phenyl*-3-*benzylcinnoline*** (XII; R = CH_2Ph) respectively in almost quantitative yields. Similar treatment of (XI), on the other hand, furnished **4-*phenyl*-3-(1′-*naphthyl*)*cinnoline*** (XII; R = 1′-naphthyl) as major product, accompanied by small amounts of a ***hydrocarbon***, $C_{24}H_{16}$, which is regarded as 2-phenylchrysene (XIII), and further investigation showed that these two types of cyclisation may become virtually mutually exclusive under suitable experimental conditions. It is thus clear that cinnoline-formation is to be regarded as a reaction which is potentially alternative to, and in competition with, any Pschorr-cyclisation arising from the diazotisation of a substance of general formula (I; R_2 = aryl).



(IX.) (X.) (XI.) (XII.) (XIII.) (XIV.)

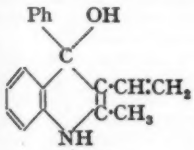
In the case of (IX) the Pschorr-cyclisation seems to be inhibited completely, because the amino-ethylene has been obtained in both the possible geometrical forms; the isomers show a strong depression of the melting point on admixture, and each of them gives 3 : 4-diphenylcinnoline in high yield under identical conditions; on the other hand, 9-phenylphenanthrene (Koelsch, *J. Amer. Chem. Soc.*, 1934, **56**, 480; Bradsher and Schneider, *ibid.*, 1938, **60**, 2960) could not be isolated from either isomer, conditions being used under which (XI) was cyclised to 2-phenylchrysene, the only recognisable product being, in each case, 3 : 4-diphenylcinnoline (in much diminished yield). This result stands in interesting contrast to that of the diazotisation of *cis*- and of *trans*-2-aminostilbene, to which reference has already been made. A further matter of interest is that each of the isomers (IX) is unaffected sterically by hot alcoholic hydrochloric acid, so there can be no doubt that the cinnoline is produced directly from two different stereoisomeric entities, and therefore, in this case at least, the cyclisation must be independent of spatial configuration. Unfortunately this point could not be established in the case of (XI), because, although two stereoisomeric amino-ethylenes, m. p.'s 145° and 183°, were again obtained, the latter was unreactive; it could not be acetylated under normal conditions, neither could it be diazotised. Although no detailed study of the actual configurations of these pairs of amino-ethylenes has been made (*e.g.*, by the nitrobenzene–iodine method of Ruggli and Dinger, *loc. cit.*), the production of 2-phenylchrysene from the diazotisable amine (XI), m. p. 145°, makes it clear that the α-naphthyl and *o*-aminophenyl nuclei occupy *cis*-positions in the latter substance.

It is obvious that the attachment of a phenyl group to the α-carbon atom of the amino-ethylene exerts an enormously powerful effect in favour of cinnoline formation, and that it overcomes the inhibitory action of an aryl group on the β-carbon atom, which is itself far from weak, as is shown by the behaviour of the 2-aminostilbenes. It is therefore surprising that no cinnoline derivatives were obtained by Mayer and Balle (*loc. cit.*) on diazotisation of (VII) and (VIII); even after allowance has been made for possible activation of the *o*- and *p*-positions by the methyl group in (VIII), the complete inhibition of cinnoline formation would scarcely be anticipated as the result of the replacement of phenyl by carboxyl on the α-carbon atom. [The work of Ruggli and his associates (*Helv. Chim. Acta*, 1936, **19**, 1288 and *loc. cit.*) has shown that a carboxyl on either the α- or the β-carbon atom has no direct effect in promoting the phenanthrene cyclisation, but that it merely directs the aryl nuclei into the necessary *cis*-positions during the synthesis of the stilbene]. It is possibly of significance that Mayer and Balle obtained the phenanthrene acid from (VII) in a yield of only 3%, in contrast to yields of the order of 75% secured in many other cases in the literature where cinnoline formation is not theoretically possible. Unfortunately the authors do not record the yield of mixed phenanthrene acids from (VIII).

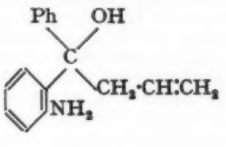
The observations recorded above show that the formation of 3 : 4-diphenyl- and of 4-phenyl-3-(1′-naphthyl)-cinnoline does not occur spontaneously. The diazotisations were carried out in strongly acid solution, followed by dilution, in contrast to the aqueous acid media employed in previous cases (Stoermer and Fincke; Simpson and Stephenson, *locc. cit.*), in which cyclisation appeared to be spontaneous. The effect of acid concentration, and of varying the group attached to the α-carbon atom of the amino-ethylene, are problems which it is hoped to investigate.

The carbinols from which (IX) and (X) were derived were prepared in high yield by the Grignard method, but the condensation of *o*-aminobenzophenone with the Grignard compound of α-chloromethylnaphthalene did not proceed smoothly, doubtless owing to the fact that considerable amounts of *s*-1 : 1′-dinaphthylethane were formed during the reaction. This hydrocarbon has previously been prepared by reduction of the amide of α-thionaphthoic acid (Bamberger and Lodter, *Ber.*, 1888, **21**, 54), and by dehydrogenation of α-methylnaphthalene with sulphur (Friedmann, *ibid.*, 1916, **49**, 277). The crude Grignard-product, after removal of hydrocarbons, yielded the unreactive amino-ethylene (XI), m. p. 183°, together with the *acetamido-carbinol*, m. p. 175°, on treatment with acetic anhydride in pyridine at 100°. The aforesaid amino-ethylene was converted into the diazotisable isomer, m. p. 145°, by means of hot alcoholic hydrochloric acid.

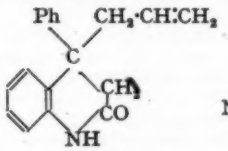
In the hope of obtaining the butadiene (XIV), *o*-aminobenzophenone was condensed with allylmagnesium bromide. An *amino-carbinol*, m. p. 72°, of the expected composition $C_{16}H_{17}ON$, was isolated in high yield, which resinified on treatment with hot dilute sulphuric acid; the resin gave an amorphous adduct with maleic anhydride. Treatment of the crude Grignard reaction product with pyridine–acetic anhydride yielded some of the neutral *acetamido-carbinol*, $C_{18}H_{19}O_2N$, but the main product was a basic *substance*, m. p. 80°, $C_{16}H_{17}ON$, which readily rearranged in hot dilute sulphuric acid to an *isomeride*, m. p. 130°. The basic character of the substance, m. p. 80°, excludes its formulation as an acetamido-ethylene; it must therefore be bicyclic, and if the *amino-carbinol* has the normal structure (XV) it can be represented either by the 3 : 4-dihydro-2-quinolone structure (XVI) or by the expression (XVII). The isomerisation to the substance, m. p. 130°, could then consist in a shift of side-chain unsaturation on the basis of (XVI), or in cyclisation of (XVII) to a tetrahydrofuran.



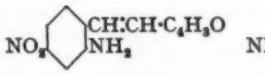
(XVII.)



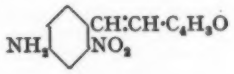
(XV.)



(XVI.)



(XVIII.)



(XIX.)

Various other modes of isomerisation, however, may be envisaged by analogy with the work of Bogert and his school (*J. Amer. Chem. Soc.*, 1934, **56**, 185, 248, 959; 1935, **57**, 151) on the cyclisation of aryl-olefins, and the constitution of the substance, m. p. 130°, must be left in abeyance until further data are available.

This work, as originally planned, included the synthesis of a number of 2-aminostilbenes with a view to varying the group on the β-ethylenic carbon atom as widely as possible. Thiele and Escales (*Ber.*, 1901, **34**, 2842) have prepared 2 : 4-dinitrostilbene by condensation of 2 : 4-dinitrotoluene with benzaldehyde in presence of piperidine, and Pfeiffer (*ibid.*, 1915, **48**, 1777) has shown that this method is of general applicability. In the present work 2 : 4-dinitrotoluene was condensed with furfural, vanillin, and piperonal. The furfurylidene *derivative* was reduced to each of the isomeric *nitro-amines* (XVIII) and (XIX); neither amine gave any crystalline product on diazotisation. In view of the results discussed above, reduction of the condensation *products* from the other aldehydes was not studied, except for a single unsuccessful experiment with the piperonylidene compound. From the method used in their formation, the amines (XVIII) and (XIX) may safely be regarded as *trans*-derivatives.

Addendum.—In Part I (Simpson and Stephenson, *loc. cit.*) it was stated that no crystalline carbinol could be obtained by the action of methylmagnesium iodide on either 5-chloro-2-amino-4′-hydroxybenzophenone or 5-chloro-2-amino-2′-hydroxy-5′-methylbenzophenone. The pure crystalline *carbinols* have now been prepared, and their properties are described in the experimental section. Each carbinol was readily dehydrated to the corresponding ethylene previously described (*loc. cit.*).

Experimental.

(Melting points are uncorrected.)

α-Phenyl-α-(2-aminophenyl)-β-(1′-naphthyl)ethylenes (XI).—A Grignard solution was prepared from magnesium (2·2 g.), ether (50 c.c.), and a solution of α-chloromethylnaphthalene (Fieser and Gates, *J. Amer. Chem. Soc.*, 1940, **62**, 2335) (14·5 c.c.) in ether (40 c.c.), which was added during 20 minutes with gentle refluxing. A solution of *o*-aminobenzophenone (4 g.) in ether (120 c.c.) was added at room temperature, and the product, after being refluxed for 1 hour, was decomposed with ice-cold ammoniacal ammonium chloride. *s*-1 : 1′-Dinaphthylethane (usually about 2 g.) crystallised from the dried and concentrated ethereal solution, and was recrystallised from benzene–alcohol, forming rosettes of colourless needles, m. p. 161—161·5° (Found: C, 93·1; H, 6·4. Calc. for $C_{22}H_{18}$: C, 93·6; H, 6·4%). The hydrocarbon is described by Bamberger and Lodter and by Friedmann (*locc. cit.*) as greenish-yellow tablets, m. p. 160°.

The filtrate from the dinaphthylethane was diluted with ether, and the amino-carbinol removed as an insoluble oily hydrochloride by extraction with 2N-hydrochloric acid. The base, liberated with ammonia and collected with ether, was a viscous resin which could not be crystallised. It was heated at 100° for 2 hours with its own weights of acetic anhydride and pyridine, and the *amino-ethylene* precipitated by slight dilution with water and scratching. The crude product was

washed with a little methanol, yielding 1·8 g. of nearly pure material, which crystallised from acetone in almost colourless glassy prisms, m. p. 182—183° (Found: C, 89·4; H, 5·85; N, 4·3. $C_{24}H_{19}N$ requires C, 89·7; H, 5·95; N, 4·4%). The amine, dissolved in a mixture of acetic and hydrochloric acids, was treated with sodium nitrite, but was recovered unchanged after addition of ammonia. As was anticipated from its method of isolation, the pure substance also failed to react with acetic anhydride in pyridine at 100°. It can be precipitated as a smeary hydrochloride by addition of hydrochloric acid to its ethereal or chloroform solution, but the strength of acid necessary for the extraction appears to depend on several factors. Thus 2N-acid will remove it readily from an ethereal solution of the crude product formed by the reaction with acetic anhydride, but repeated shaking with concentrated acid was necessary to remove the base from a mixture of it and *s*-1 : 1′-dinaphthylethane dissolved in chloroform.

The dehydration of the amino-carbinol with acetic anhydride was not always complete. In an experiment using 8 g. of *o*-aminobenzophenone, the total basic material was treated as above with pyridine and acetic anhydride, and then separated into neutral and basic fractions with ether and hydrochloric acid. The neutral fraction gave about 3·3 g. of the *acetamido-carbinol*, which formed colourless needles, m. p. 175—176°, from aqueous alcohol (Found: C, 82·0; H, 6·15; N, 4·1. $C_{26}H_{23}O_2N$ requires C, 81·9; H, 6·1; N, 3·7%). The basic fraction was almost pure amino-ethylene (3·2 g.).

The foregoing amino-ethylene was refluxed for 1½ hours with 40 vols. of a mixture of equal parts of concentrated hydrochloric acid and alcohol; the *isomeride*, then precipitated by addition of ammonia, separated from aqueous alcohol in small soft needles, m. p. 144—145° (yield, 60—65%) (Found: C, 89·3; H, 6·0; N, 4·8. $C_{24}H_{19}N$ requires C, 89·7; H, 5·95; N, 4·4%).

2-Phenylchrysene (XIII).—(*a*) A solution of the amino-ethylene, m. p. 144°, (0·5 g.) in acetic acid (5 c.c.) and concentrated hydrochloric acid (3·5 c.c.) was treated at 0° with 2½% aqueous sodium nitrite (8 c.c.). (A brownish-red solution of the diazonium salt was formed, which gave a red insoluble product when a few drops of the solution were added to alkaline β-naphthol solution.) The clear diazonium solution was diluted with water (20 c.c.), and on slight warming of the resulting turbid solution a solid was gradually precipitated, which was recrystallised from slightly aqueous methanol-acetone. The product (330 mg.) was digested with a little hot aqueous alcohol, and the small insoluble fraction crystallised from a large volume of alcohol, yielding slightly discoloured leaflets of *2-phenylchrysene*, m. p. 192—192·5° (Found: C, 94·7; H, 5·8. $C_{24}H_{16}$ requires C, 94·7; H, 5·3%).

(*b*) A solution of the diazonium salt (from 1 g. of amine) was divided into two equal parts. One portion was poured slowly (5 mins.) into excess of a slightly warm solution of sodium acetate in which was suspended 0·2 g. of copper powder. After a few minutes the precipitate was collected, washed, dried, and extracted with hot ethyl acetate–alcohol (charcoal). The filtered extract, on concentration to a small volume, deposited 0·19 g. of 2-phenylchrysene, m. p. 180—185°, which after two crystallisations from ethyl acetate formed discoloured leaflets, m. p. 192—193° alone and when mixed with the specimen described in (*a*). No other compound was isolated from the mother-liquors; an exhaustive search was not made, but it is certain that the corresponding cinnoline (*q.v.*) could not have been present in appreciable quantity.

4-Phenyl-3-(1′-naphthyl)cinnoline (XII, R = α-$C_{10}H_7$).—The second portion of the diazonium solution mentioned above was diluted with water (1½ vols.) and left for a few hours at room temperature. The precipitate that had gradually formed was collected, washed, and crystallised from aqueous alcohol after removal of a few mg. of insoluble material, presumably 2-phenylchrysene; one further crystallisation yielded the *cinnoline* (270 mg.) in almost pure condition, m. p. 174—176°. The same substance was also obtained from the first alcoholic filtrate from the 2-phenylchrysene described in (*a*) above; comparison of the two experiments showed that warming the diazonium solution after dilution diminished slightly the yield of cinnoline in favour of hydrocarbon. The pure cinnoline separated from aqueous alcohol in brittle yellow polyhedra, m. p. 178—179° (Found: C, 87·2; H, 4·4; N, 8·3. $C_{24}H_{16}N_2$ requires C, 86·75; H, 4·85; N, 8·4%).

Phenylbenzyl-2-aminophenylcarbinol.—A solution of *o*-aminobenzophenone (2 g.) in ether (60 c.c.) was added to a Grignard solution prepared from magnesium (1·1 g.), benzyl chloride (5·5 g.), and ether (30 c.c.). After being refluxed for ¾ hour, the reaction product was decomposed as already described. On concentration of the washed and dried ethereal solution, the almost pure *carbinol* rapidly crystallised (2·2 g.), and after recrystallisation from methanol formed faintly yellow, glassy prisms, m. p. 150—150·5° (Found: C, 83·0; H, 6·75; N, 5·4. $C_{20}H_{19}ON$ requires C, 83·0; H, 6·6; N, 4·8%).

α-(2-Aminophenyl)-αβ-diphenylethylenes (IX).—The above carbinol (750 mg.) was heated at 100° with 25 c.c. of aqueous sulphuric acid (20% by volume), the originally clear solution soon becoming turbid. After ¾ hour the reaction mixture was made alkaline with ammonia, and the product, which solidified on scratching, crystallised from aqueous alcohol, yielding 0·42 g. of fairly pure *amino-ethylene*; after several crystallisations the base formed clusters of cream-coloured prismatic needles, m. p. 113—114° (Found: C, 88·75; H, 6·2; N, 5·4. $C_{20}H_{17}N$ requires C, 88·5; H, 6·3; N, 5·2%).

On a larger scale, 6·7 g. of the amino-carbinol gave 2·4 g. of amino-ethylene, m. p. 113—114°. The earlier recrystallisation liquors were combined and concentrated. On standing, a further crop (2·1 g.), m. p. 85—95°, separated; after several crystallisations from methyl alcohol the isomeric *amino-ethylene* was obtained in clusters of hard short prisms, m. p. 102—104°, and 85—90° when mixed with its geometrical isomeride (Found: C, 88·35; H, 6·2; N, 5·55%).

Each of the amino-ethylenes, after being refluxed for 2 hours in alcohol and concentrated hydrochloric acid (1 : 1, 40 parts), was recovered unchanged on addition of ammonia. The hydrochloride of the amine, m. p. 113—114°, was easily soluble in alcohol; that of the isomer, m. p. 102—104°, was sparingly soluble.

3 : 4-Diphenylcinnoline (XII, R = Ph).—(*a*) Each of the foregoing compounds was diazotised under the conditions already described for the amino-ethylene (XI), m. p. 145°. Dilution with water caused an immediate precipitation of *3 : 4-diphenylcinnoline*. The crude product, which was formed in virtually quantitative yield, had m. p. 148—150°, and on recrystallisation from aqueous methanol formed dense yellow rhombs, m. p. 149—150° (Found: C, 85·2; H, 5·4; N, 9·8. $C_{20}H_{14}N_2$ requires C, 85·1; H, 5·0; N, 9·9%).

(*b*) In attempts to effect cyclisation to 9-phenylphenanthrene, each of the isomers, m. p. 113° and 102°, was diazotised as rapidly as possible under the same conditions as before, and the solutions were then poured into excess of aqueous sodium acetate at *ca.* 80°, containing *ca.* 0·2 g. of copper powder in suspension. After being warmed for a few minutes, the suspensions were set aside for some hours, filtered, and extracted with chloroform–ether. The extracts, which contained no phenolic material, yielded respectively 40% and 35% of 3 : 4-diphenylcinnoline, m. p. and mixed m. p. 149—150°; no other crystalline substance could be isolated from the oily mother-liquors.

Phenyl-2-aminophenyl-β-phenylethylcarbinol.—β-Phenylethylmagnesium bromide [from 3·3 g. of magnesium, 21 c.c. of β-phenylethyl bromide (Norris, Watt, and Thomas, *J. Amer. Chem. Soc.*, 1916, **38**, 1071), and 100 c.c. of ether] and *o*-aminobenzophenone (6 g. in 160 c.c. of ether) yielded a gummy product, which was isolated by the method already described. When an ethereal solution of it was shaken with 2N-hydrochloric acid, an oily hydrochloride was thrown out, which was basified with ammonia and extracted with ether. The residue (8·9 g.) from the dried and evaporated solution crystallised on standing, and after several crystallisations from aqueous alcohol the *carbinol* (5 g.) was obtained in short prismatic needles, m. p. 97—98° to an opaque liquid which cleared at 102° (Found: C, 82·4; H, 6·8; N, 5·1. $C_{21}H_{21}ON$ requires C, 83·1; H, 7·0; N, 4·6%).

Treatment of the crude resinous product from the Grignard reaction with pyridine–acetic anhydride yielded the N-*acetyl* derivative of the carbinol, which crystallised from benzene–acetone in clusters of fine colourless needles, m. p. 168—168·5° (Found : C, 80·0; H, 6·8; N, 4·15. $C_{23}H_{23}O_2N$ requires C, 79·95; H, 6·7; N, 4·1%).

α-Phenyl-α-(2-aminophenyl)-β-benzylethylene (X).—Dehydration of the carbinol was effected with 10% sulphuric acid (20 vols.) at 100° for ½ hour. The *amine* crystallised from aqueous alcohol in clusters of needles, m. p. 108—109° (yield, 33%) (Found : C, 88·3; H, 6·9; N, 5·1. $C_{21}H_{19}N$ requires C, 88·4; H, 6·7; N, 4·9%).

4-Phenyl-3-benzylcinnoline (XII, R = CH_2Ph).—A solution of the amino-ethylene (X) (0·5 g.) in glacial acetic acid (5 c.c.) and concentrated hydrochloric acid (4 c.c.) was diazotised with 2½% aqueous sodium nitrite at 0°. After 10 minutes, water (10 c.c.) was added, and the solution warmed to 40—50°. Unlike previous analogues, this *cinnoline* showed markedly basic properties, as it was not precipitated until the solution was made alkaline with ammonia. It formed pale yellow, prismatic needles (yield, almost quantitative), m. p. 116·5—118°, from alcohol (Found : C, 85·1; H, 5·25; N, 9·65. $C_{21}H_{16}N_2$ requires C, 85·1; H, 5·4; N, 9·5%).

Phenyl-2-aminophenylallylcarbinol (XV) *and Derivatives.*—(*a*) Allylmagnesium bromide (from 2·2 g. of magnesium, 10 c.c. of allyl bromide, and 50 c.c. of ether) and *o*-aminobenzophenone (4 g. in 90 c.c. of ether) gave a red suspension; in similar reactions, this generally indicated incomplete reaction with the amino-ketone, and addition of a further 3 c.c. of allyl bromide and 0·5 g. of magnesium produced the usual pale yellow suspension. This was worked up in the usual manner and yielded a viscous resin (5 g.), which was heated for 2 hours at 100° with 3 c.c. each of pyridine and acetic anhydride; water was then added, the product extracted with ether, and the extract was washed, first with water, and then with 2N-hydrochloric acid. Basification of the acid washings with ammonia gave an oil (3·13 g.), which was collected with ether; it crystallised almost completely from slightly aqueous alcohol, yielding the *substance* (XVI) or (XVII) as cream-coloured rods, m. p. 79—80° after several crystallisations (Found : C, 81·65, 82·1; H, 6·65, 6·7; N, 5·55, 5·6. $C_{18}H_{17}ON$ requires C, 82·1; H, 6·5; N, 5·3%).

(*b*) The original ethereal solution, from which the foregoing substance was removed with hydrochloric acid, was washed with aqueous sodium carbonate and water, dried, and evaporated. A solution of the residue in ether–ligroin deposited the N-*acetyl* derivative (0·7 g.) of the amino-carbinol (XV) in clusters of prisms, m. p. 129—130° after crystallisation from benzene–ligroin (Found : C, 76·9; H, 6·7; N, 5·2. $C_{18}H_{19}O_2N$ requires C, 76·85; H, 6·8; N, 5·0%). After being refluxed for 3 hours with 10% alcoholic potassium hydroxide, it yielded the amino-carbinol (XV), m. p. 67—69° from ether–ligroin (yield, 50%), identified by mixed m. p. with the specimen described in (*c*).

(*c*) An ethereal solution of the crude resinous carbinol from 6 g. of *o*-aminobenzophenone was shaken with 2N-hydrochloric acid, and the base, liberated from the acid washings with ammonia, was extracted with ether. A solution of it in benzene–ligroin deposited dense prisms (4·5 g.) of the *amino-carbinol*, m. p. 70—72° after recrystallisation [45—50° when mixed with the substance, m. p. 80°, described in (*a*)] (Found : C, 80·6; H, 6·75; N, 6·05. $C_{18}H_{17}ON$ requires C, 80·3; H, 7·15; N, 5·85%).

(*d*) A solution of the compound (1·2 g.), m. p. 80°, in aqueous sulphuric acid (5% by volume; 24 c.c.) was heated at 100° for ¼ hour, the originally clear solution becoming oily almost immediately. The *isomeride* was liberated by addition of ammonia, and separated from aqueous alcohol in short well-formed needles (0·8 g.), m. p. 129·5—130·5° (Found : C, 82·0; H, 6·35; N, 5·5. $C_{18}H_{17}ON$ requires C, 82·1; H, 6·5; N, 5·3%).

(*e*) A solution of the amino-carbinol (XV) (300 mg.) in 5% aqueous sulphuric acid (6 c.c.) was kept at 100° for 25 minutes, after which ammonia was added to the still clear solution, and the precipitated oil collected with ether. Benzoylation of this material in pyridine gave a resin, from which *ca.* 50 mg. of the N-*benzoyl* derivative of the amino-carbinol were isolated (needles), m. p. (after crystallisation from aqueous alcohol) 173—174° alone and mixed with an authentic specimen (m. p. 173·5—175°) (Found : C, 80·75; H, 6·0; N, 4·25. $C_{23}H_{21}O_2N$ requires C, 80·4; H, 6·15; N, 4·1%).

Condensations of 2 : 4-*Dinitrotoluene with Aldehydes.*—Freshly-distilled furfural (50 c.c.), 2 : 4-dinitrotoluene (100 g.), and piperidine (5 c.c.) were heated under an air-condenser at 120—130° (bath temp.) for 1 hour, and then at 130—140° for a further hour. The mass was digested with a mixture of equal volumes of ethyl acetate and alcohol, filtered cold, and the product crystallised from ethyl acetate, from which the *furfurylidene* compound (47 g.) separated in orange-brown prismatic needles, m. p. 135—136°, easily soluble in acetone and hot acetic acid, and almost insoluble in alcohol (Found : C, 55·5; H, 3·2; N, 11·25. $C_{12}H_8O_5N_2$ requires C, 55·4; H, 3·1; N, 10·8%). The reaction was incomplete, the crude product smelling strongly of furfural; increasing the length of time or the temperature of the reaction, however, produced considerable decomposition. On the other hand, analogous condensations with piperonal and vanillin proceeded smoothly, and yielded *products* which crystallised respectively in lustrous, brick-red, brittle prisms, m. p. 179·5—180·5°, sparingly soluble in alcohol, acetone, chloroform, acetic acid, and ethyl acetate, but easily soluble in hot *cyclo*hexanone (Found : C, 57·55; H, 3·3; N, 9·05. $C_{15}H_{10}O_6N_2$ requires C, 57·3; H, 3·2; N, 8·9%), and small scarlet prisms, m. p. 191—191·5°, moderately soluble in hot ethyl acetate (Found : C, 57·0; H, 4·1; N, 9·0. $C_{15}H_{12}O_4N_2$ requires C, 57·0; H, 3·8; N, 8·9%).

α-Nitroaminophenyl-β-(2-furyl)ethylenes (XVIII and XIX).—(*a*) The foregoing dinitrophenylfurylethylene (6 g.) was dissolved in acetic acid (90 c.c.) and treated at 95—100° with iron filings (4·5 g.), added in 10 portions during 20 minutes with frequent shaking; two additions of 10 c.c. portions of water were made at intervals of 5 and 10 minutes from the start of the experiment. Reduction was rapid, and an iron oxide sludge was formed. The solution was diluted with water (2 vols.), and the sludge and the decanted liquid extracted separately with ether. The combined extracts were washed with very dilute hydrochloric acid, sodium carbonate solution, and water, dried, and evaporated, and the residue taken up in methyl alcohol. The *nitroamine* (1·2 g.) rapidly separated in crimson needles, m. p. 130·5—131·5° after recrystallisation; it dissolved in benzene to a yellow, and in methanol to an intensely red, solution (Found : C, 62·3; H, 4·75; N, 12·6. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4; N, 12·2%). The N-*acetyl* derivative, prepared with acetic anhydride–pyridine at 100°, crystallised from aqueous acetone in sheaves of yellow silky needles, m. p. 214—215° (Found : C, 61·5; H, 4·95; N, 10·75. $C_{14}H_{12}O_4N_2$ requires C, 61·7; H, 4·45; N, 10·3%).

Diazotisation of the nitroamine was carried out under the conditions already described, but in this case the hydrochloride was insoluble in the mixed acid medium. Gradual addition of excess of aqueous sodium nitrite did not bring about solution; instead, a brown amorphous product was formed, which, after some hours, was collected, suspended in benzene–ether, and separated by means of aqueous ammonia into a small neutral fraction and a dark amorphous fraction partly soluble in alkali. The neutral ether-soluble fraction, after chromatographic purification, yielded undiazotised nitroamine (0·1 g. from 0·65 g.); the aqueous suspension, after slight concentration in presence of sodium hydroxide, was acidified, but the precipitated material could not be crystallised either from solvents or by the use of the chromatographic method.

(*b*) Hydrogen sulphide was passed for ½ hour, with shaking, into a warm suspension of the dinitro-compound (10 g.) in alcohol (150 c.c.) and concentrated aqueous ammonia (15 c.c.), and the red solution set aside overnight. It was then concentrated somewhat and filtered from inorganic matter. On evaporation to a small volume, followed by cautious addition of water, the *nitroamine* (yield, 50—55%) separated in purple-red blades or deep scarlet needles, m. p. 86—88° after recrystallisation (aqueous methanol); amorphous matter was removed if necessary by extracting the crude product with ether, in which the nitroamine is soluble (Found : C, 62·4; H, 4·75; N, 12·45. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4;

N, 12·2%). The N-*acetyl* derivative, prepared by the usual method, separated from aqueous methanol in long, brittle, orange-brown needles, m. p. 168·5—169·5° (Found: C, 61·25; H, 4·7; N, 10·35. $C_{14}H_{12}O_4N_2$ requires C, 61·7; H, 4·45; N, 10·3%).

A solution of the nitroamine in 10 parts of acetic acid gave, like its isomer, an insoluble yellow hydrochloride on addition of 6 parts of concentrated hydrochloric acid. Diazotisation yielded a soluble diazonium salt (dark red solution), which did not form a cinnoline, because the solution (i) evolved nitrogen on warming alone or with copper powder, and (ii) gave a purple precipitate and a red solution on pouring into alkaline β-naphthol and sodium phenoxide solution respectively.

Carbinols from Methylmagnesium Iodide and Chloroaminohydroxybenzophenones.—The condensations of methylmagnesium iodide with (*a*) 5-chloro-2-amino-4′-hydroxybenzophenone and (*b*) 5-chloro-2-amino-2′-hydroxy-5′-methylbenzophenone were carried out substantially as previously described (*loc. cit.*), but the products were isolated by pouring into iced ammoniacal ammonium chloride. The ethereal extracts were washed with water, dried, and evaporated, and the residues crystallised respectively from aqueous alcohol and ether–ligroin. The *carbinol* from (*a*) formed large dense prisms (4·1 g. from 6 g. of amino-ketone), m. p. 173—174° (Found: C, 63·8; H, 5·1; N, 5·6. $C_{14}H_{14}O_2NCl$ requires C, 63·7; H, 5·35; N, 5·3%). Reaction (*b*) yielded a *carbinol* (9·3 g. from 11·5 g. of amino-ketone) which separated from aqueous alcohol in small, very pale yellow prisms, m. p. 117—118·5° (Found: C, 65·65; H, 6·05; N, 5·3. $C_{15}H_{16}O_2NCl$ requires C, 64·9; H, 5·8; N, 5·0%), and 90—100° when mixed with the related ethylene (m. p. 108°). Each carbinol was dehydrated by aqueous sulphuric acid at 100° to the corresponding amino-ethylene (yields, 75% and 50% respectively).

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DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, May 14th*, 1943.]

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121. *The* Senecio *Alkaloids. Part I. Rosmarinine.*

By (MISS) MARGARET F. RICHARDSON and FRANK L. WARREN.

Rosmarinine, isolated originally from *Senecio rosmarinifolius* Linn., has now been found in other *Senecio* species. *S. hygrophilus* R. A. Dyer and C. A. Sm. is conspecific with "*S. adnatus*" DC. of de Waal and Tiedt, who isolated platyphylline; but the alkaloid content varies: rosmarinine, platyphylline, and an *alkaloid* $C_{18}H_{27}O_6N$, m. p. 176°, have been isolated as sole constituents or as mixtures, depending on stage of growth, season and district.

Rosmarinecine, now obtained crystalline, is assigned a structure (II or III). Senecic acid, found free in the plant and obtained by hydrolysis of platyphylline and rosmarinine, is isolated as its open-chain form and as the monolactone. The identity of platynecic acid and senecic acid is confirmed.

DURING investigations on the *Senecio* alkaloids we have isolated rosmarinine, first obtained from *S. rosmarinifolius* Linn. by de Waal (*Onderstepoort J. Vet. Sci. and An. Ind.*, 1940, **15**, 241), from *S. brachypodus* DC., *S. pauciligulatus* R. A. Dyer and C. A. Sm., and *S. hygrophilus* R. A. Dyer and C. A. Sm. (descriptions of the last two to appear in *J. South African Bot.*). The last named is conspecific with specimens erroneously identified as *S. adnatus* DC. (Nat. Herb. Nos. 27,025 and 27,026), from which de Waal and Tiedt (*ibid.*, p. 251) isolated platyphylline, one of the alkaloids originally isolated from *S. platyphyllus* DC. (Orékhov and Tiedebel, *Ber.*, 1935, **68**, 650).

In view of the discrepancy the *S. hygrophilus* was collected over a wide area and at different stages of growth. de Waal collected his material in 1939 near Mount Ayliff, East Griqualand. From material collected at Weza, E. Griqualand, we also isolated only platyphylline; but from plants growing in the environs of Pietermaritzburg, two alkaloids were usually found, and in one district rosmarinine alone was found. These findings are summarised in the table, in the obtaining of which a standard procedure was adopted for the extraction of at least one kilogram; and the results are reproducible to the accuracy given.

Date, 1941.	District.	Growth stage.	Platyphylline, %.	Rosmarinine, %.
Oct. 5th	G	Pre-budding	0·8	0·3
Oct. 31st	G	Budding	0·15	0·1
Oct. 31st	M	Budding	0·2	0·03
Oct. 31st	M	Budding (shade)	0·5	trace
Nov. 12th	M	Flowering	0·1	0·05
Nov. 21st	D	Flowering	none	1·5
Dec. 22nd	W	Flowering	0·5	none

G, Greenhill, near Richmond, Natal; M, between Nel's Rust and Greenhill; D, Duncairn, Pietermaritzburg; W, Weza, between Harding and Kokstad, East Griqualand.

It will be noted that the plant is richest in alkaloid prior to budding, as was observed for "*S. latifolius*" by Watt (J., 1909, **95**, 466), and when growing in the shade. Variations of the alkaloidal content with the season are recorded for the *Senecio* species by Barger and Blackie (J., 1936, 743; 1937, 584).

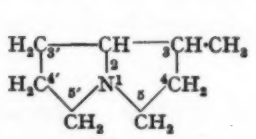
Material collected in 1940 from Duncairn yielded a new *alkaloid*, $C_{18}H_{27}O_6N$, m. p. 176°; but as the season advanced, the amount of this alkaloid diminished and finally gave way to small quantities of rosmarinine. The new alkaloid crystallised from benzene with two molecules of solvent of crystallisation, which were lost on standing. This power of forming a molecular compound with benzene is not shared by either platyphylline or rosmarinine. There was, however, a possibility of a combination similar to that of "homoquinone" (cupreine–quinine); but even after prolonged boiling of equimolecular portions of the two alkaloids with benzene none of the new alkaloid was isolated, whereas the two individuals were separated quantitatively.

Senecic acid was found free in the plant, and the accumulation of material from these investigations has permitted a more careful study of its properties. It has been isolated now as a hydroxy-dicarboxylic acid as well as the lactone, both of which show considerable stability (cf. Barger and Blackie, J., 1936, 744). Evaporation with a drop of hydrochloric acid converts the acid into the lactone. The differences in the recorded melting points and the difficulties in purification (Manske, *Canadian J. Res.*, 1939, **17**, 1) may have been due to the mixture. We failed to detect any fumaric acid as recorded for several species by Manske (*ibid.*, 1936, **14**, 6).

Rosmarinine was characterised by hydrolysis to senecic acid and rosmarinecine, the latter of which, previously isolated as an oil even after regeneration from the picrate (de Waal, *Onderstepoort J. Vet. Sci. and An. Ind.*, 1941, **16**, 157), has now been obtained as a crystalline solid, m. p. 171—172° (corr.). Platyphylline gives platynecine and senecic acid as shown by de Waal (*loc. cit.*), the platynecic acid of Orékhov and Tiedebel (*loc. cit.*) being identical with senecic acid lactone.

Rosmarinecine, $C_8H_{15}O_3N$, is a tertiary amine, and readily forms a *methiodide*, m. p. 189° (corr.). It is saturated in that it is not reduced by sodium amalgam or catalytically in the presence of Adams's catalyst. The existence of a methylpyrrolizidine nucleus (I) for several *Senecio* alkaloids would indicate that rosmarinecine is a trihydroxy-derivative of methylpyrrolizidine, with which the formula, $C_8H_{12}N(OH)_3$, agrees. The hydroxy-groups cannot occupy the 2-, 5- or 5′-positions. A hydroxy-group in position 2 might be expected to be reduced by a type of Emde degradation (cf. Briggs, Newbold, and Stone, J., 1942, 7), and a system containing hydroxyl groups in position 5 or 5′ would be capable of anionotropic change similar to cotarnine, and would be reducible. Furthermore, it does not form *O*-alkyl compounds when heated with alcohols (cf. Blount and Robinson, J., 1932, 2305) and does not condense with nitromethane (cf. Hope and Robinson, J., 1911, **99**, 2119). In addition, rosmarinecine is not oxidised by periodic acid; therefore no two hydroxy-groups are on neighbouring carbon atoms.

This leaves only two possibilities, (II) and (III), of which that with the hydroxy-group in the 3′-position (II) is favoured, since this shows a close connection between the modified formulæ of platynecine and retronecine (Adams, Carmack, and Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2593; Adams and Hamlin, *ibid.*, p. 2597). Thus rosmarinecine is probably 3′ : 4-*dihydroxy*-3-*hydroxymethylpyrrolizidine* (II), and such a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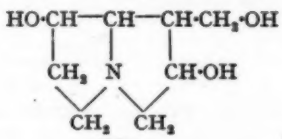
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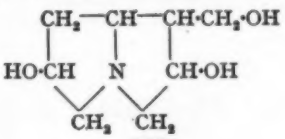
(III.)

formula would represent rosmarinecine as hydroxyplatynecine, a conclusion that would find support in the close association in the plant of rosmarinine and platyphylline, which are esters of senecic acid with rosmarinecine and platynecine respectively. Dehydration between positions 3 and 4 would give retronecine.

Experimental.

On account of the confusion that has arisen in the identification of South African *Senecio* species, the National Herbarium Number and the Collector's Number will always be quoted in this series of papers.

Extraction.—The dried, ground plant material (2 kg.) was extracted (Soxhlet) with 95% alcohol, the extract concentrated to 2 l., a solution of citric acid (15 g.) in water (250 c.c.) added, and the alcohol removed in a vacuum. The black viscous mass was diluted to 1 l. and kept for 3 days, and the fatty material collected. The addition of the citric acid solution before the complete removal of the alcohol causes the fatty material to become granular, and facilitates the removal of the alkaloid. If this procedure were not adopted, the alcohol was only difficultly removed from the intractable sticky mass. The filtrate was extracted many times with ether to remove acids, the dissolved ether removed by bubbling air rapidly through the solution, and this then extracted with chloroform, which caused copious precipitation of gummy material. The filtered material was made alkaline with ammonia and extracted with chloroform. The chloroform extract was evaporated to a small bulk, a few drops of methanol added, and the residual solvent blown off. The solidification of the alkaloid was facilitated by the addition of a few drops of acetone. Only occasionally was it necessary to redissolve the material in citric acid and regenerate it. The ethereal solution gave the necic acid.

S. hygrophilus R. A. Dyer and C. A. Sm. (Nat. Herb. No. 26,456 and 26,457; Warren 84 and 163).—The crude alkaloid was stirred to a thick paste with acetone and filtered. The solid was reshaken with cold acetone, collected, and crystallised from acetone or ethanol to give shining laminæ of rosmarinine, m. p. 209° (corr.), $[\alpha]_D^{24°}$ − 91·5° (1% in methanol) (Found: C, 61·3; H, 7·5; N, 4·1. Calc. for $C_{18}H_{27}O_6N$: C, 61·2; H, 7·7; N, 4·0%). de Waal (*Onderstepoort J. Vet. Sci. and An. Ind.*, 1940, **15**, 245) gives m. p. 208° (corr.), $[\alpha]_D^{20°}$ − 94°. The acetone washings gave platyphylline, which separated from ethanol in rhombic crystals, m. p. 129° (corr.), and showed no depression on admixture with a specimen supplied by de Waal (Found: N, 4·3. Calc. for $C_{18}H_{27}O_5N$: N, 4·2%). Orékhov and Tiedebel (*loc. cit.*) give m. p. 124°; de Waal 129° (corr.). The perchlorate had m. p. 226° (corr.); Orékhov and Tiedebel give 222—223°.

Flowering plant material collected in 1940 gave an *alkaloid* which separated from acetone in rhombic crystals, m. p. 175—176° (corr.), $[\alpha]_D^{25°}$ − 62·4° (1½% in methanol) (Found: C, 61·4; H, 7·6; N, 4·3. $C_{18}H_{27}O_6N$ requires C, 61·2; H, 7·7; N, 4·0%). Flowering aerial portion gave 0·1% yield calculated on dried material. Crystallisation from benzene gave stout prisms containing $2C_6H_6$, which were given up on standing to leave an amorphous powder (Found: loss at 40° in a vacuum, 28·7. Calc. for $C_{18}H_{27}O_6N,2C_6H_6$: loss, 30·6%).

Ethereal extract gave 0·03% of senecic acid.

S. pauciligulatus R. A. Dyer and C. A. Sm. (Warren 128A in Nat. Herb., Pretoria).—This gave 1% of pure rosmarinine,

m. p. 209° (corr.) (Found: C, 61·2; H, 7·8; N, 4·2. Calc. for $C_{15}H_{27}O_6N$: C, 61·2; H, 7·7; N, 4·0%). Ethereal extract gave 0·3% of senecic acid.

S. brachypodus D.C. (Nat. Herb. No. 26,502; Warren 199).—This gave rosmarinine, m. p. 209° (corr.), showing no depression with the specimens above (Found: N, 4·0%). Roots gave 0·24%, flowering aerial portion 0·36%, calculated on dried material. Ethereal extract gave 0·17% of senecic acid.

Hydrolysis of Rosmarinine.—Rosmarinine (10 g.; 1 mol.) was refluxed with hydrated barium hydroxide (14 g.; 1·6 mols.) and water (200 ml.) for 1 hour. The solution was filtered and made just acid to phenolphthalein with 25% sulphuric acid, and the barium sulphate separated centrifugally. The solution was evaporated to dryness, and the residue exhaustively extracted with absolute alcohol. The extract was evaporated to dryness, the gum taken up in water, 25% sulphuric acid added drop by drop till all traces of barium had been precipitated, and the filtered solution evaporated on a water-bath to leave a pale yellow gum which partly crystallised on standing. The whole was taken up in a little dry pyridine, and the solid frozen out at − 10° and recrystallised from pyridine to give rosmarinecine in stout prisms, m. p. 171—172° (corr.), $[\alpha]_D^{25°}$ − 118·5° (Found: C, 55·5; H, 8·8; N, 8·2. Calc. for $C_8H_{15}O_3N$: C, 55·45; H, 8·7; N, 8·1%). The picrate had m. p. 175° (corr.); de Waal gives m. p. 175° (corr.) (Found: N, 14·1. Calc. for $C_8H_{15}O_3N,C_6H_3O_7N_3$: N, 13·9%).

The solid after extraction with alcohol was worked up as described by de Waal (*Onderstepoort J. Vet. Sci. and An. Ind.*, 1941, **16**, 157) to give *senecic acid*, m. p. 151° (corr.) (to a turbid liquid), $[\alpha]_D^{25°}$ + 11·8° (2% in ethanol) (Found: C, 55·5; H, 7·5; equiv., 109. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·5%; equiv., 108). The dibasic acid was evaporated twice to dryness with dilute hydrochloric acid, and the resulting solid crystallised from benzene to give fine silky needles of senecic acid lactone, m. p. 156° (corr.) (Found: equiv., 202. Calc. for $C_{10}H_{14}O_4$: equiv., 198). Manske (*Canadian J. Res.*, 1939, **17**, 1) gives for the lactone m. p. 154°.

Rosmarinecine Methiodide.—Rosmarinecine (1·2 g.) in methanol was heated with excess of methyl iodide for 20 mins., the solvent removed in a vacuum, and the residue crystallised from methanol to which a little dry ether was added to give colourless needles of *rosmarinecine methiodide*, m. p. 195° (corr.) (Found: N, 4·4. $C_8H_{15}O_3N,CH_3I$ requires N, 4·4%).

Attempted Oxidation.—Rosmarinecine (0·1 g.) in water (10 ml.) was left for 90 mins. with 0·1M-periodic acid (10 ml.); iodometric estimation of periodic acid then showed no change in concentration. A repetition at 40° similarly showed no oxidation.

Attempted Condensation.—Rosmarinecine (0·1 g.), ethanol (1 ml.), and nitromethane (5 drops) were kept for one hour and heated. The product gave a picrate from alcohol, m. p. 175° (corr.), not depressed by rosmarinecine picrate.

The authors acknowledge a grant from the National Research Council for the purchase of apparatus, and the invaluable help given by Mr. C. A. Smith in the collection and identification of the plant material.

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122. *The Nature of the Amino-group in Aminoacridines. Part I. Evidence from Electrometric Studies.*

By ADRIEN ALBERT and REGINALD GOLDACRE.

The striking differences in antiseptic powers among the five monoaminoacridines (Rubbo, Albert, and Maxwell, *Brit. J. Exp. Path.*, 1942, **23**, 69) prompted this search for such evidence of individuality as would account for the biological variations encountered.

In this Part, the relative basicities of these and related compounds are examined, and it is found that the structure of 2- and 5-aminoacridines permits of a greater degree of resonance in the ion than occurs in the un-ionised base. Hence, these isomerides show an abnormally high degree of ionisation, an effect that parallels their high biological activity. The properties of the other isomerides suggest that they are fairly normal amino-derivatives of acridine.

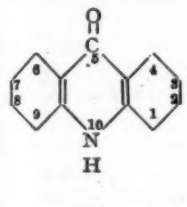
SINCE little is known about the structure of amino-derivatives of nitrogenous heterocyclic nuclei, the present work was undertaken to gather such information in respect of a series of isomerides, the five aminoacridines, the members of which show marked biological individuality (Rubbo, Albert, and Maxwell, *loc. cit.*), since, whilst 1-amino-acridine has less antiseptic activity than acridine, the 3- and the 4-isomeride are more, and the 2- and the 5-isomeride outstandingly more, bactericidal than acridine (Table I). This part deals with the relative basicities of the five aminoacridines, their acetyl derivatives, methobromides, and hydroxy-analogues, and of some acids derived from 2-aminoacridine.

The data in Table I were obtained by potentiometric titration with the glass electrode. Every endeavour was made to use water as the solvent because of its biological importance, but in many cases the curves showed irregularities which were attributed to a series of long-delayed equilibria due to hydrochloride being carried down by the poorly soluble (and often glutinous) base on liberation. They were reminiscent of the calcium phosphate curves obtained by Wendt and Clark (*J. Amer. Chem. Soc.*, 1923, **45**, 882). As Bennett and Glasstone (J., 1935, 1821) believe that a series of bases preserves the same order of basicity in dilute alcohols, recourse was had when necessary to 67% methanol and 50% ethanol, which, by keeping all the components in solution throughout the titration, achieved good equilibria (Fig. 1). In our experience the pK values obtained with these two solvents are practically identical but average 0·5 unit lower than the corresponding values in water (when derived from regular curves; see also Mizutani, *Z. physikal. Chem.*, 1925, **118**, 327).

Acridine was found to be a weak base, similar in strength to aniline ($2·7 \times 10^{-10}$) and rather weaker than pyridine ($1·1 \times 10^{-9}$), these data being due to Britton and Williams (J., 1935, 796) (glass electrode, in water at 18°). The closeness of the values for pyridine and acridine would suggest that the benzene rings of the latter exert little influence on the central ring.

In the hydroxyacridines, too, the influence of the benzene and the pyridine rings on one another appears small. The 1-, 2-, 3-, and 4-hydroxyacridines do not differ greatly in basicity from one another or from acridine, whereas *p*-aminophenol is much more basic than its *m*-isomeride or aniline (Kuhn, *Helv. Chim. Acta*, 1928, **11**, 7). Again, the acidic strengths of 2-, 3-, and 4-hydroxyacridines are similar to one another and to that of phenol (contrast *p*-aminophenol, Kuhn, *loc. cit.*). 1-Hydroxyacridine is somewhat weaker as an acid, possibly because of an " ortho "-effect (see below).

In 5-hydroxyacridine (" acridone "), where the hydroxyl group is attached to the ring containing the nitrogen atom, a considerable interaction between them is shown by the relative absence of basic and acidic properties. This substance has a high m. p. (354°) and lacks marked phenolic or ketonic properties. Its similarities to 4-hydroxypyridine (Arndt and Kalischek, *Ber.*, 1930, **63**, 587, 2963) show it to be a resonance hybrid of acridone (I) and the otherwise unstable internal salt (II) of 5-hydroxyacridine.



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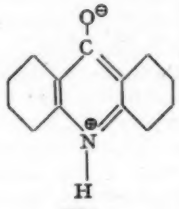

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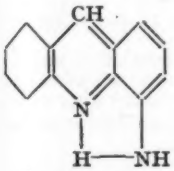

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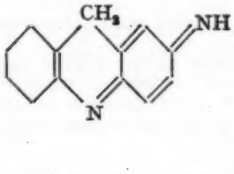
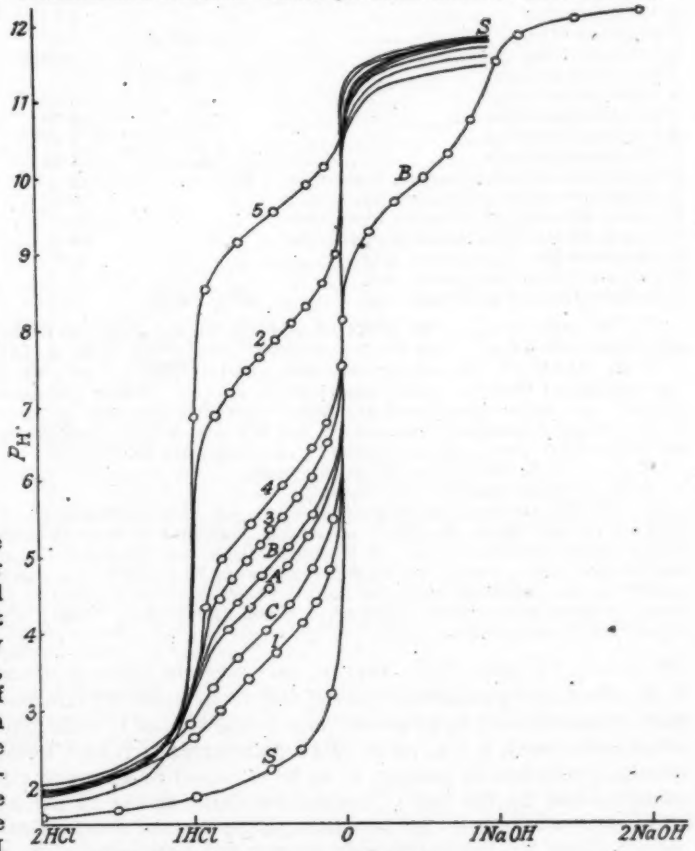


(IV.)

FIG. 1.

Potentiometric Titration Curves [in dilute alcohols as in Table I].



1 = 1-*Aminoacridine.*
2 = 2- ,,
3 = 3- ,,
4 = 4- ,,
5 = 5- ,,

A = *Acridine.*
B = *2-Hydroxyacridine.*
C = *3-Acetamidoacridine.*
S = *Blank*; 50% C_2H_5OH (*by vol.*).

Concerning the aminoacridines, we are indebted to our colleagues, Messrs. Mellor and Craig (Sydney) and Smith and Turnbull (Melbourne) for spectroscopic evidence that it is the *ring* nitrogen that becomes quaternary when these substances form monoacid salts, so the well-known weakness (as a base) of $-NH_2$ attached to a highly conjugated system (*e.g.*, anthracene) is seen also in the acridine series. From analogy with the hydroxyacridines, an amino-group in the benzene rings should have little influence on the basicity of the ring nitrogen, and Table I shows that this is the case with 1-, 3-, and 4-aminoacridines which, on chemical evidence (Part II) must be considered typical amino-derivatives of acridine. Although 3- and 4-aminoacridines are slightly stronger than acridine, yet 1-aminoacridine is seven times weaker as a base, and chemically somewhat less reactive (Part II). These data are consistent with the assumption that the two nitrogens are linked by hydrogen (as in III; cf. 8-acetamidoquinoline, Chaplin and Hunter, J., 1938, 375), but so little is known of the N–H–N bond and so many 1 : 2-diamines have a lower basicity than the corresponding monoamines (cf. ethylenediamine, Britton and Williams, *loc. cit.*; *o*-phenylenediamine and 2 : 3-diaminonaphthalene, Kuhn, *loc. cit.*) that it is sufficient to say that 1-aminoacridine shows a decided " ortho "-effect. It should be noted that 3-aminoacridine cannot have the imine structure (IV) because the 5 : 5-dimethyl derivative of (IV) is a typical imine, readily hydrolysed by water (Goldstein and Kopp, *Helv. Chim. Acta*, 1928, **11**, 478).

The remaining aminoacridines, the 2- and the 5-isomeride, are distinguished by their remarkable strength as bases. This appears to be due to a heightened resonance effect in the ion which, in the case of 5-aminoacridine, would be a hybrid to which the structures (V*a*), derived from the normal form of the base, and (V*b*), derived from a tautomeric form (V*c*), contribute. Similar structures (VI*a*, *b*, *c*) may be written for 2-aminoacridine. These are examples of a phenomenon, discussed by Branch and Calvin (" The Theory of Organic

TABLE I.

Dissociation constants of acridine and derivatives.

Substance (0·0005 g.-mol. in 20—30 ml.).	Solvent.*	pK_a at 20°.†	K_b.‡	p$K_{a'}$ at 20°.	$K_{a'}$.§	*B*.‖
Acridine	67% MeOH	4·54	3×10^{-10}	—	—	1·2
1-Hydroxyacridine	50% EtOH	4·18	1×10^{-10}	10·70	2×10^{-11}	—
2-Hydroxyacridine	,,	4·86	6×10^{-10}	9·86	1×10^{-10}	—
3-Hydroxyacridine	,,	4·21	1×10^{-10}	9·68	2×10^{-10}	—
4-Hydroxyacridine	,,	4·45	2×10^{-10}	9·40	3×10^{-10}	—
5-Hydroxyacridine	,,	<2	—	>12	—	—
1-Aminoacridine	67% MeOH	3·67	4×10^{-11}	—	—	0·8
2-Aminoacridine	,,	7·60	3×10^{-7}	—	—	4·2
3-Aminoacridine	,,	5·30	2×10^{-9}	—	—	1·6
4-Aminoacridine	,,	5·74	5×10^{-9}	—	—	1·8
5-Aminoacridine	,,	9·34	2×10^{-5}	—	—	4·6
2-Aminoacridine	50% EtOH	7·67	4×10^{-7}	—	—	—
5-Aminoacridine	,,	9·38	2×10^{-5}	—	—	—
1-Acetamidoacridine	67% MeOH	2·5	3×10^{-12}	—	—	0·6
2-Acetamidoacridine	,,	5·12	1×10^{-9}	—	—	0·8
3-Acetamidoacridine	,,	4·18	1×10^{-10}	—	—	1·2
4-Acetamidoacridine	,,	3·87	6×10^{-11}	—	—	0
5-Acetamidoacridine	,,	3·83	6×10^{-11}	11·1	8×10^{-12}	0
2-Amino-10-methylacridinium hydroxide	H_2O	>12	—	—	—	3·8
3-Amino-10-methylacridinium hydroxide	,,	9·8	—	—	—	—
4-Amino-10-methylacridinium hydroxide	,,	10·0	—	—	—	—
5-Amino-10-methylacridinium hydroxide	,,	10·1	—	—	—	4·8
2-Aminoacridine-7-carboxylic acid	,,	2·3	2×10^{-12}	8·0	1×10^{-8}	0
2-Aminoacridine-7-sulphonic acid	,,	<2	—	7·7	2×10^{-8}	0
2-Aminoacridine-7-sulphonamide	50% EtOH	6·7	5×10^{-8}	10·9	1×10^{-11}	1·6

* The correction for the effect of alcohols on the glass electrode has not been subtracted but is of the order of only 0·04 unit (Dole, "The Glass Electrode," New York, 1941, p. 141).

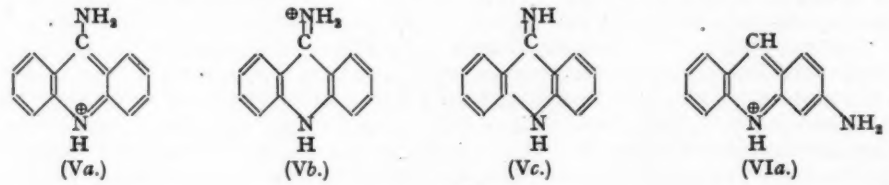
† K_a stands for the acidity constant, $(B)(H^+)/(BH^+)$. pK_a was taken as the pH of half-neutralisation and was also calculated from five other points of the curves. Where necessary it has been corrected for hydrolysis of the salt formed. In water, on account of delayed equilibria (see text) apparent pK_a values were obtained for acridine and 1-, 2-, 3-, 4-, and 5-aminoacridines of 4·3, 4·0, 8·1, 5·1, 5·5, and 9·5, respectively. 5-Acetamidoacridine has been corrected for sodium-ion error (+0·1 unit at pH 11; Dole, *op. cit.*, p. 129).

‡ K_b = First basic dissociation constant.

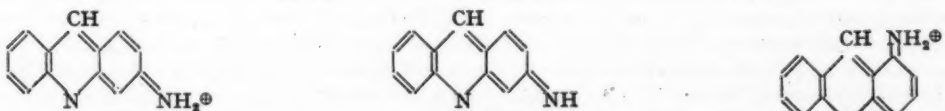
§ $K_{a'}$ = Acid dissociation constant.

‖ *B* is the averaged bacteriostatic index, *i.e.*, the average value of the inhibition of growth of five organisms (*Cl. Welchii, Strept. Hæm.* A, *Staph. aureus, B. coli*, and *Proteus vulgaris*) after incubation at 37° for 48 hours, in 10% serum-broth adjusted to pH 7·2 (Rubbo, Albert, and Maxwell, *loc. cit.*). As this index is expressed in powers of 2, 4-aminoacridine is twice and 5-aminoacridine is 14 ($= 2^{3\cdot8}$) times as effective as 1-aminoacridine. A biological paper shortly to be published with Dr. Rubbo shows that, in a series of forty acridines, an index higher than 2·5 is given only by those compounds which have a pK higher than 7 and, hence, are at least 50% ionised at the biologically important value, pH 7·2.

Chemistry," Prentice-Hall, 1941, p. 194), wherein a base is stronger than would otherwise have been predicted if its structural pecularities permit the acquisition of extra resonance forms on passing into the ion. This phenomenon is seen in its purest form in the case of 1 : 5-diaminopentamethine (VII) and its alkyl derivatives which may reach a pK value of 12 (Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162). A less intense exaltation of basicity is to be expected in aromatic structures because the extra ionic resonance is usually offset by the loss of nuclear resonance in one of the ionic structures. This balancing of resonance effects leaves a net gain for 5-aminoacridine ion, the symmetrical structure of the central ring being the determining factor (cf. the analogously constituted 4-aminopyridine, pK 9·1). A smaller net gain is shown by the 2-aminoacridine ion, whereas the low basicity of 4-aminoacridine indicates that there would be no increase in resonance energy in passing from the base to an ion of which the *o*-quinonoid structure (VIII) was a component. These concepts are proving useful in the prediction of basicity for other heterocyclic amines.



(Va.) (Vb.) (Vc.) (VIa.)



(VIb.) (VIc.) (VIII.)

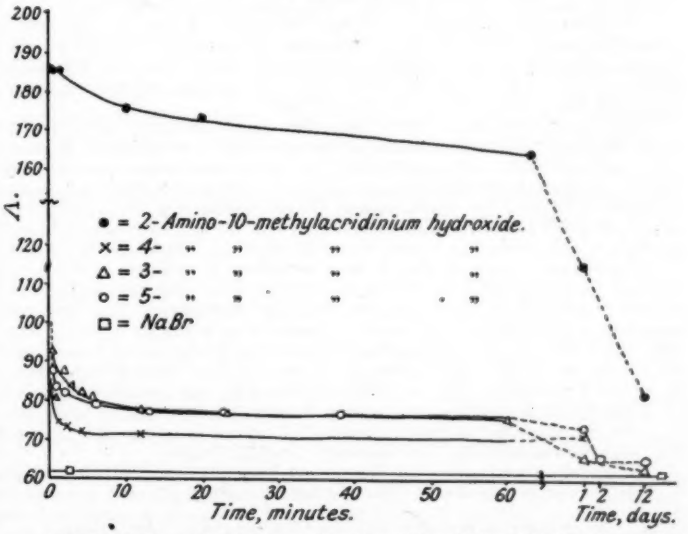
(VII.) $NH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}\overset{\oplus}{N}H_2$

Spectrometric investigation in highly acid solution (see Experimental) showed that the pK_a values corresponding to second basic dissociation constants for the 1-, 3-, and 4-aminoacridines and the 3- and 4-amino-10-methylacridinium hydroxides lay between 0·5 and 1·2 approximately. On the other hand, the monoacid salts of 2- and 5-aminoacridines and of their methochlorides gave no colour change in this range. This supports the theory of extra ionic resonance for these substances, since in passing from mono- to di-acid salts, the pairs of resonant ionic structures (V*a* and *b*; VI*a* and *b*) would be destroyed.

The values obtained for the acetamidoacridines (Table I) show that acetylation of the amino-group effects a decrease in basicity in every case. This is most marked in the 2- and the 5-isomeride, since the imino-form (V*b* and VI*b*) of the ions becomes too weak a base on acetylation to contribute much to the base-strengthening resonance. These substances have slight acidic properties also, particularly the 5-isomeride.

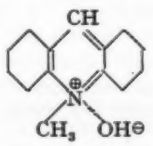
The behaviour of quaternary heterocyclic amines on alkalisation is unpredictable, and no adequate explanation can be advanced for the diverse behaviour of the methobromides of the aminoacridines when made alkaline (Fig. 2). Table I shows 2-amino-10-methylacridinium hydroxide to be a quite strong base, and conductivity measurements at 0° (see Experimental) show that it is ionised to the extent of approximately 90% at M/256 and so is almost as strong a base as sodium hydroxide. This isomeride, in fact, is almost as stable as 2 : 8-diamino-10-methylacridinium hydroxide which resists boiling for a few minutes. Fig. 2 shows that the other isomerides undergo a rapid transformation to pseudo-bases as found by Hantzsch and Kalb for 10-methylacridinium chloride (*Ber.*, 1899, **32**, 3109), which undergoes the change (IX) ⟶ (X). Hence the pK_a values given for the 3-, 4-, and 5-isomerides in Table I are only nominal, representing equilibrium values for this reversible reaction. Aston (*J. Amer. Chem. Soc.*, 1931, **53**, 1448) questions Hantzsch's interpretation of the drop in conductivity found when methylacridinium salts are treated with alkalis and attributes it to the precipitation of a quaternary ammonium hydroxide. Hantzsch's explanation, however, fits our compounds quite well, especially the 4-isomeride, whose violet solution gives a yellow precipitate with alkali. The 3- and the 4-isomeride on shaking with phosphate buffer at pH 7·3 in the Warburg apparatus rapidly took up oxygen to form, presumably, 3- and 4-amino-10-methylacridones. The 2- and the 5-isomeride were stable under these conditions. All attempts to prepare 1-amino-10-methylacridinium salts were unsuccessful.

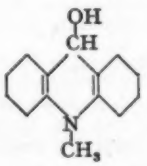
FIG. 2.



Conductivities of mixtures of amino-10-methylacridinium bromides and sodium hydroxide at 0° in M/256-solution. The 5-isomeride gives a precipitate at once, the 3-isomeride after some minutes, the others after several hours.

(IX.)





(X.)

The introduction of a carboxylic or sulphonic acid group into 2-aminoacridine has produced a mutual weakening of the manifest acid and basic properties to a degree intermediate between that seen in glycine and *p*-aminobenzoic acid on the one hand and taurine and sulphanilic acid on the other (cf. Sidgwick, " Organic Chemistry of Nitrogen," Oxford, 1937, p. 108).

EXPERIMENTAL.

Materials.—The acridine was purified by steam-distillation and had m. p. 110°. The aminoacridines were prepared according to Albert and Ritchie (*J. Soc. Chem. Ind.*, 1941, **60**, 120), and the 2-aminoacridine-7-sulphonic acid and -7-sulphonamide according to Aarons and Albert (J., 1942, 183). The acetamidoacridines were prepared by heating the aminoacridines (3 g.) in acetic anhydride (6 ml.) for 30 mins. at 105°, pouring the mixture into benzene, filtering off the solid, and treating it with aqueous ammonia. After recrystallisation from dilute alcohol, white or yellow bases were obtained which gave yellow or brown salts. The m. p. found for 4-acetamidoacridine (230°; 237°, corr.) is higher than that previously recorded (225—226°).

5-Acetamidoacridine, white crystals from 40 parts of absolute alcohol, m. p. 266° (276°, corr.), did not fluoresce in solution (Found : N, 11·7. $C_{15}H_{12}ON_2$ requires N, 11·85%). The acetyl group is not in the 10-position since methyl toluene-*p*-sulphonate gives a product which yields 5-amino-10-methylacridinium bromide (Part II) on hydrolysis.

The preparation of the hydroxyacridines and quaternary salts is given in Part II.

2-Aminoacridine-7-carboxylic acid. 2-Chloro-4-nitrobenzoic acid (20 g.; 0·1 mol.), *p*-aminobenzoic acid (20·1 g.; 0·15 mol.), sodium acetate (16·4 g., 0·2 mol.), catalytic copper (1 g.), and butanol (200 ml.) were refluxed for 4 hours, treated with excess sodium carbonate and steam-distilled. The contents of the flask were acidified, filtered at the boil, and the cake washed with boiling water then recrystallised from alcohol (150 ml.). *5-Nitrodiphenylamine-2 : 4'-dicarboxylic acid* was thus obtained (15% yield) as reddish-brown crystals, m. p. 281° (Found : N, 9·1. $C_{14}H_{10}O_6N_2$ requires N, 9·25%). This acid was refluxed for 2 hours with phosphorus oxychloride (15 ml.), poured into water, made strongly alkaline, and boiled for 15 mins. *2-Nitroacridone-7-carboxylic acid* was obtained (95% yield) on acidification as an orange powder, not melting below 360° (Found : N, 9·8. $C_{14}H_8O_5N_2$ requires N, 9·9%). To this acid (3 g.), dissolved in water (150 ml.) with sodium hydroxide (0·66 g.; 1·5 equiv.), was added freshly amalgamated aluminium foil (1·5 g.; 2 equivs.) during 45 mins. at 100°. After filtration, the cake was boiled with water (75 ml.), and the bulked filtrates acidified with concentrated hydrochloric acid (2·7 ml.). The 2-aminoacridane-7-carboxylic acid was oxidised in this solution by boiling with the theoretical amount of ferric chloride. After filtering and cooling, the hydrochloride of 2-aminoacridine-7-carboxylic acid separated as orange needles which were recrystallised from boiling water with a trace of acid. Treatment with sodium acetate solution gave the *acid* in 45% yield; scarlet solid, retaining water of crystallisation when dried at 110°, losing it at a higher temperature and decomposing at about 200° without melting (Found : N, 10·7. $C_{14}H_{10}O_2N_2,H_2O$ requires N, 10·9%). It was sparingly soluble in alcohol with a green fluorescence, and dissolved in alkalis with a brown colour and green fluorescence.

Potentiometric Titrations.—These were carried out by running N-hydrochloric acid into a solution of the base (0·0005 g.-mol. in 20—30 ml.), followed, when necessary, by N-sodium hydroxide. The solution was contained in a beaker fitted with an efficient stirrer, glass electrode, and a potassium chloride–agar bridge connected to a calomel half-cell and a Leeds and Northrup universal pH potentiometer set. The latter was checked against buffer solutions at pH 2·20, 4·00, 7·00, 8·00, 9·00, and 10·00.

Conductances.—These were measured in an ordinary Arrhenius cell placed in a Wheatstone bridge circuit (using A.C. supplied by a valve-oscillator) similar to that of Grinnell Jones and Josephs (*J. Amer. Chem. Soc.*, 1928, **50**, 1049). The cell-constant of the platinised platinum electrodes was determined by means of N/10-potassium chloride at 0°. Each amino-10-methylacridinium bromide (20 ml. of N/32-solution) was placed successively in the cell, and further dilutions obtained by withdrawing 10 ml. portions with a calibrated pipette and adding 10 ml. of water. This was repeated until the molecular conductivity at 0° became approximately constant, which occurred in the range M/256—M/1024. The following values were obtained for the 2-, 3-, 4-, and 5-isomerides respectively : 57, 56, 56, 51.

The curves shown in Fig. 2 were obtained by adding N/128-sodium hydroxide as quickly as possible to the same volume of M/128-solution of the above bromides, the cell and all solutions being maintained at 0°, and the mixture gently stirred by raising and lowering the electrodes. Care was taken to exclude carbon dioxide throughout. The percentage dissociation of 2-amino-10-methylacridinium bromide was calculated as follows, after Hantzsch and Kalb (*loc. cit.*). The Λ_{256} of the methobromide was 57, which is equivalent by Onsager's equation to $\Lambda_0 = 60$. Subtracting 41 for the Λ_0 of Br^- at 0°, the Λ_0 of the 2-amino-10-methylacridinium ion becomes 19, whilst by adding 118 for the Λ_0 of OH^-, the value of $\Lambda_0 = 137$ is obtained for the methohydroxide at 0°. The observed value of Λ_{256} for the mixture of methobromide and sodium hydroxide was 185, and taking from this 62 for the Λ_{256} of sodium bromide, the observed Λ_{256} for the methohydroxide becomes 123, and it is hence 123/137, or 90%, dissociated. The values for Br^-, OH^- and Na^+ were obtained from International Critical Tables.

An approximate value for the *second basic dissociation constant* was obtained with the help of the Hilger–Nutting Visible Spectrophotometer. Each substance (0·01 g.) was dissolved in N/50-acid (5 ml.) and, by means of a micropipette, 0·2 ml. of each solution was added in turn to a range of buffers (Clark's potassium chloride–hydrochloric acid solutions) of pH 0·1, 0·4, 0·7, 1·0, 1·2, 1·4, and 2·0. By plotting the extinction coefficients at pH 2·0 and at pH 0·1 against wave-lengths, it became possible to choose a wave-length for which the difference in absorption between these two solutions was maximal. The intensity of this wave-length at pH 2·0 was compared with its intensity in other buffers. The pH of half-change is given in Table II, from which it is deduced that the second basic dissociation constant in these cases approximates to 1×10^{-13}.

TABLE II.

Substance.	Wave-length chosen, A.	pH of mid-point in colour-change between mono- and di-acid salts.
1-Aminoacridine	4700	0·5
3-Aminoacridine	4800	1·1
3-Amino-10-methylacridinium hydroxide	5300	1·2
4-Aminoacridine	5250	0·6
4-Amino-10-methylacridinium hydroxide	5500	0·7

We thank Professor J. C. Earl, whose help and encouragement have made this series of studies possible, also Mr. E. G. Griffiths, Dr. T. Iredale, and Mr. D. P. Mellor for the interest in this section of the work. The Trustees of the Commonwealth Science Grant are thanked for substantial financial support to one of us (A. A.).

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123. *The Nature of the Amino-group in Aminoacridines. Part II. Evidence from Chemical Reactions.*

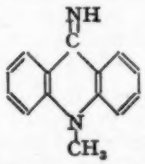
By ADRIEN ALBERT and BRUCE RITCHIE.

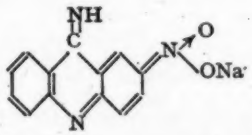
Examination of the chemical reactions of the five monoaminoacridines revealed no correlation as striking as that between ionisation and antisepsis (Part I). Nevertheless, the biologically outstanding isomerides (5-, 2-, and 1-) showed the greatest chemical individuality, particularly the first, which behaved distinctively on diazotisation, alkaline hydrolysis, hydrogenation, reaction with aldehydes and with methyl iodide.

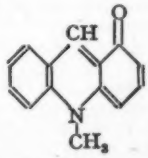
Because of the highly electrophilic nature of the acridine nucleus, the amino-group was readily detached from the salts of all the isomerides by aniline and by acid at 160°.

Reactions with Aldehydes.—When refluxed in alcohol with benzaldehyde, 3- and 4-aminoacridines gave almost quantitative yields of the anils, but the 1- and 2-isomerides reacted only to a small extent, and the 5-isomeride not at all. Salicylaldehyde, which reacts more vigorously with amines, gave a quantitative yield with the 2-isomeride, but the 5- still failed to react. The abnormally low reactivity of 2- and 5-aminoacridines suggests that in alcohol they exist in equilibrium with non-reacting imino-forms (VI*c* and V*c*, Part I). Since 4-amino-2-phenylquinoline reacts with salicylaldehyde (Feist and Kulinski, *Arch. Pharm.*, 1936, **274**, 310), the total lack of activity of 5-aminoacridine is attributed to a summation of this tautomeric effect and a steric hindrance akin to cases noted by Jensen and Rethwisch (*J. Amer. Chem. Soc.*, 1928, **50**, 1144), *viz.*, acridine-5- and 3-methylquinoline-4-carboxylic acids, which, unlike quinoline-4-carboxylic acid, cannot be esterified with alcohol and acid. In its slow reactivity with benzaldehyde, 1-aminoacridine gives further evidence of the " ortho-effect " (Part I).

Action of Methyl Iodide.—When 1-, 2-, 3-, and 4-aminoacridines were refluxed with methyl iodide in methanol (acridine does not methylate under these conditions), only the primary amino-group became methylated. On the other hand, 5-aminoacridine gave an almost quantitative yield of *5-amino-10-methylacridinium iodide*, which may also be regarded as the hydriodide of *5-imino-10-methylacridane* (XI), into which it is reversibly converted on basification. 4-Aminoquinoline and 4-aminopyridine also methylate on the ring nitrogen under these conditions (Tschitschibabin, *Ber.*, 1921, **54**, 822; 1925, **58**, 1708) and it is likely that in all these cases the usually unreactive tertiary ring nitrogen is reacting as a secondary amine, because of tautomerism (V*c*, Part I). The above acridane compound is incapable of tautomerism and sufficiently resembles " 5-amino-acridine " in colour and fluorescences as to suggest that the latter is really 5-iminoacridane (V*c*, Part I). (*5-Dimethylaminoacridine* differs markedly from these substances, but *5-methylaminoacridine* is similar.) Another case of prototropy involving an imino-group in the 5-position is provided by *3-nitro-5-aminoacridine* (red), which gives the purple nitronate (XII) with alcoholic alkali, whereas 2-nitro-5-aminoacridine, in which rearrangement of bonds is impossible, gives no colour change.

(XI.) 

(XII.) 

 (XIII.)

Methylation on the ring nitrogen takes place at 180° with 2-, 3-, 4-, and 5-acetamidoacridines, but the 1-isomeride does not react because of the " ortho-effect."

Diazotisation.—Although 2-, 3-, and 4-aminoacridines diazotised and coupled normally, as did their 10-methobromides, yet 1-aminoacridine formed a precipitate with sodium nitrite and hydrochloric (or acetic) acid and did not couple with β-naphthol. The analogously constituted 8-aminoquinoline, however, diazotised and coupled normally. 5-Aminoacridine and its methobromide did not diazotise by the more usual methods, but highly acid conditions (cf. 4-aminopyridine; Königs, *Ber.*, 1924, **57**, 1175) were effective and an intense red colour was obtained with alkaline β-naphthol. This resistance to diazotisation apparently arises from the high ionic resonance of the monoacid salts of 5-aminoacridine which do not allow of true $-\overset{\oplus}{N}H_3$ groups arising in any quantity.

Hydrogenation.—On hydrogenation (Raney nickel), the aminoacridines all added two atoms of hydrogen but at different rates and always more slowly than acridine itself. As will be seen from the table below, the rate of reduction places the isomerides in the same order as their basicity, and 2 : 5-diaminoacridine, presumably because of its higher basicity ($pK = 10{\cdot}5$), shows marked resistance to hydrogenation. Dr. B. Breyer of this University informs us that aminoacridines require highly negative potentials for polarographic reduction and the reaction is thermodynamically irreversible. 3-Aminoacridane has now been obtained analytically pure and has characteristics different from those assigned to it in the literature.

Total absorption of hydrogen (ml.) at 760 mm. and 20° of 1 g. of acridine compound and 1 g. of Raney nickel catalyst (itself responsible for 10 ml.) in 98% alcohol. (The monoaminoacridines require 120 ml. for 2H; acridine requires 130 ml.)

Substance. Time (mins.).	2.	5.	10.	20.	40.	60.	80.	120.	180.
Acridine	65	125	137	140	140				
1-Aminoacridine	—	65	90	120	132	135	135		
3-Aminoacridine	—	—	55	85	120	127	135	135	
4-Aminoacridine	—	—	55	85	120	127	135	135	
2-Aminoacridine	—	—	—	40	65	85	95	120	135
5-Aminoacridine	—	—	—	—	50	65	75	95	125
2 : 5-Diaminoacridine	—	—	—	—	—	—	5	7	10

Action of Alkali.—When the aminoacridines were boiled with 5N-potassium hydroxide, 5-aminoacridine alone was hydrolysed, evolving ammonia and giving 11% of 5-hydroxy-acridine in 2 hours. Similarly, 5-methylamino- and 5-dimethylamino-acridines gave 24 and 68% yields, respectively. On the other hand, 2-aminoacridine could be fused with moist sodium hydroxide for 2 hours at 200° without decomposition.

Action of Aniline and of Acid.—When the hydrochlorides of the five aminoacridines were refluxed with aniline, or heated with concentrated hydrochloric acid (2 hours at 160—200°), ammonia was split out and the corresponding phenylaminoacridines or hydroxyacridines, respectively, formed. No special significance attaches to the differences in yields obtained, as it was not possible to devise conditions where homogeneity was identical. However, all ten reactions went with a readiness that reveals an attraction exerted by the highly conjugated acridine nucleus on the electrons forming the $\overset{\oplus}{C}$–NH_3 bond in the salts. This electrophilic effect is small in the benzene ring but larger in the naphthalene and the quinoline series (cf. Franzen and Kempf, *Ber.*, 1917, **50**, 101; Claus and Howitz, *J. pr. Chem.*, 1893, **47**, 432; **48**, 177). *2-Phenylaminoacridine* was thus prepared by a method excluding contamination with the 4-isomeride, and melts 55° higher than Besthorn and Curtman's specimen (*Ber.*, 1891, **24**, 2042).

Experimental.

Reactions with Aldehydes.—The aminoacridine (1 g.) and benzaldehyde (0·6 g. = 1·1 mol., freed from acid and redistilled) or salicylaldehyde (0·7 g., similarly purified) were refluxed in alcohol (15 ml.) for 1½ hours. Only in the case of the 1-isomeride did a deposit form during the reaction. The mixture was made alkaline with sodium carbonate solution, steam-distilled until no more aldehyde passed over, and cooled. The solid was filtered off, dried in a vacuum, and analysed by steam-distilling a portion (1 g.) in the presence of excess dilute sulphuric acid into a known amount of N/2-hydroxylamine hydrochloride, previously made neutral to methyl-orange. The hydrochloric acid liberated by the aldehyde was back-titrated with N/2-sodium hydroxide, with constant shaking. The yield of anil was calculated from these analyses, whereas pure specimens were obtained in duplicate experiments. *1-Benzylideneaminoacridine* (28% yield), yellow crystals from benzene on addition of light petroleum, m. p. 149° (151° corr.); the yield is greatly increased if one drop of piperidine is used as a catalyst (cf. Glen, Sutherland, and Wilson, J., 1936, 1484) (Found: N, 9·9. $C_{20}H_{14}N_2$ requires N, 9·9%). 2-Benzylideneaminoacridine (20% yield) resisted purification. *2-Salicylideneaminoacridine* (95% yield), orange crystals from alcohol, m. p. 229° (236° corr.) (Found: N, 9·2. $C_{20}H_{14}ON_2$ requires N, 9·4%). *3-Benzylideneaminoacridine* (86% yield), yellow crystals from *cyclo*hexane or methanol, m. p. 148° (Found: N, 10·0%). *4-Benzylideneaminoacridine* (92% yield), orange crystals from 50 parts of alcohol, m. p. 179° (182° corr.) (Found: N, 10·1%).

1-Nitroacridine was prepared (Jensen, *J. Amer. Chem. Soc.*, 1927, **49**, 1049) by treating the black condensate from 2-aminobenzaldehyde and *o*-bromonitrobenzene with sulphuric acid. It was later found that the black condensate could be recrystallised from ether (60% yield) in long, orange needles, m. p. 120°, of *2-nitrodiphenylamine-2′-aldehyde* (Found: C, 64·6; H, 4·0. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·2%).

Action of Methyl Iodide.—Acridine (0·9 g.), 1-nitroacridine (1·3 g.), and the five aminoacridines (0·97 g.) were severally refluxed with methyl iodide (2·9 g., 4 equivs.) and methanol (2·9 g.) for 4 hours. The first two were practically unchanged, but 1-, 2-, 3-, and 4-aminoacridines gave uncrystallisable mixtures of partly methylated products that were completely precipitated by ice-cold N/20-sodium carbonate and were hence free from quaternary compounds. On the other hand, 5-aminoacridine deposited 5-amino-10-methylacridinium iodide in 85% yield on cooling, and this, after being washed free from a little 5-dimethylaminoacridine with acetone, was recrystallised from 80 parts of water, giving bright yellow crystals, m. p. *ca.* 305° (decomp.). These were treated with cold, dilute sodium hydroxide, and the precipitate, dried at 130°, was identified as 5-imino-10-methylacridane (see p. 461) of which the m. p. and mixed m. p. were identical with those of a specimen prepared from the methylation of 5-acetamidoacridine (see below). The methiodide or the imine, boiled for an hour with N/20-sodium carbonate, was quantitatively decomposed into ammonia and 10-methylacridone (m. p. and mixed m. p. with authentic specimen, 202°).

Methylation of Acetamidoacridines.—Nitrobenzene (100 ml.) was heated to 180°, and the appropriate acetamidoacridine (10 g.) and methyl *p*-toluenesulphonate (10 g.; 1·25 mols.) added. The mixture was stirred at 180° for ½ hour, cooled, treated with benzene (250 ml.), and filtered after a day. The precipitate, which in no case contained a diazotisable amine, was washed with benzene and heated with hydrobromic acid (60 ml. of 25% HBr) on the water-bath for 2 hours. The hydrolysate was neutralised with sodium hydroxide, chilled well, and the crude amino-10-methylacridinium bromide filtered off, dissolved in water (500 ml.) at 50°, treated with sodium bicarbonate (2 g.), filtered at 50° from tar and unmethylated product, and finally mixed with hydrobromic acid (2·7 ml. of 48% HBr) and well chilled. After separation of the crystals, a second crop was obtained by concentration. 1-Acetamidoacridine and 1-nitroacridine were not methylated by this method, the latter being partly oxidised to 1-nitroacridone. Acridine was methylated quantitatively.

2-Amino-10-methylacridinium bromide was further purified by dissolution in water (200 ml.) and treatment at room temperature with sodium carbonate (2·5 g.), a tarry impurity being coagulated on charcoal before filtering. The filtrate was acidified with hydrobromic acid, chilled, and the bright scarlet crystals (75% yield) recrystallised from 1·5 parts of water (charcoal) (90% recovery); m. p. 236° (243° corr.; sealed tube). They were soluble in water, giving an orange solution having an intense green fluorescence when dilute (Found: C, 55·3; H, 4·9; N, 9·0; Br, 26·0. $C_{14}H_{13}N_2Br,H_2O$ requires C, 54·7; H, 4·9; N, 9·1; Br, 26·05%). Sodium hydroxide at high temperatures, but not at 0°, gives an immediate precipitate of the carbinol base. The bromide diazotises and couples with β-naphthol to give an intense blue precipitate, soluble in alcohol to a port-wine coloured solution.

3-Amino-10-methylacridinium bromide was finally recrystallised from water (10 parts) or alcohol (60 parts); yield, 70% of red crystals giving a red, non-fluorescent solution in water (Found: C, 58·3; H, 4·5; N, 9·8. $C_{14}H_{13}N_2Br$ requires C, 58·1; H, 4·5; N, 9·7%). Diazotisation and coupling with β-naphthol gives a port-wine colour. Sodium hydroxide instantly gives a yellow precipitate of the carbinol base which dissolves in ether and regenerates the original substance on acidification. *4-Amino-10-methylacridinium bromide* was finally recrystallised from water (30 parts); yield, 80% of violet crystals, m. p. 267° (sealed tube). It gives a purple, non-fluorescent solution in water, but is only sparingly soluble in alcohol (blue solution) (Found: C, 54·8; H, 4·8; N, 9·3%). Diazotisation and coupling with β-naphthol gave a brownish-red colour. Sodium hydroxide acts as with the 3-isomerides. Both the 3- and the 4-isomeride are dibasic, giving yellow bromide-hydrobromides with excess of hydrobromic acid. The 2- and the 5-isomeride are only monobasic. *5-Amino-10-methylacridinium bromide* was finally recrystallised from boiling water (8 parts); yield, 75% of yellow crystals, m. p. approx. 305° (decomp.). It dissolves in 50 parts of cold water to a yellow solution with a greenish-blue fluorescence that becomes pure blue on dilution (Found: C, 58·2; H, 4·4; N, 9·85%). Sodium hydroxide (but not ice-cold sodium carbonate) instantly liberates the yellow carbinol base, *5-amino-5-hydroxy-10-methylacridane*, which is very soluble in cold alcohol with a green fluorescence, becoming blue on dilution (Found, for material dried in a vacuum at 20°: C, 74·6; H, 6·1. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%). The bright yellow aqueous solution is only faintly alkaline. When boiled with dilute sodium carbonate it evolves ammonia and is entirely

converted into 10-methylacridone in an hour. When dried at 130° for 30 mins., it gives *5-imino-10-methylacridane* (XI), an orange substance, m. p. 134—136° (sealed tube), very soluble in benzene (Found: C, 80·5; H, 5·7. $C_{14}H_{13}N_2$ requires C, 80·8; H, 5·8%). Both the anhydro- and the carbinol-base regenerate the original salt with acid.

5-Chloro-3-nitroacridine (B.P. 441,007) was treated with ammonium carbonate in phenol as described for 5-chloro-2-nitroacridine (Albert and Gledhill, *J. Soc. Chem. Ind.*, 1942, **61**, 159); yield, 93% of *3-nitro-5-aminoacridine hydrochloride*, which was recrystallised from 55 parts of water, forming bright yellow crystals, soluble in 300 parts of cold water without fluorescence (Found: C, 56·8; H, 3·8; N, 15·3. $C_{13}H_9O_2N_3$,HCl requires C, 56·6; H, 3·7; N, 15·2%). The base is bright red and melts at *ca.* 300° (decomp.). It is sparingly soluble in benzene with a green fluorescence that is abolished by a drop of alcohol. The temperature gradients in nitrobenzene and 60% aqueous pyridine are good. Although insoluble in aqueous sodium hydroxide, it gives a purple colour (XII) and green fluorescence in N-alcoholic sodium hydroxide.

When this was reduced with nascent ferrous carbonate (cf. Albert and Gledhill, *loc. cit.*), 3 : 5-*diaminoacridine* was obtained (75% yield) as orange crystals from dilute alcohol, m. p. 229—230° (sealed tube), moderately soluble in boiling water and very soluble in alcohol to a yellow solution with a green fluorescence (Found: C, 74·2; H, 5·4; N, 20·0. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%). The hydrochloride is very soluble in water to an orange, non-fluorescent solution and is precipitated by alcohol. Excess of concentrated hydrochloric acid produces a colourless solution with a violet fluorescence, as happens with the 2 : 5-isomeride (dihydrochloride formation). The sulphate is sparingly soluble. The salts diazotise and couple with β-naphthol (red).

5-Methylaminoacridine.—5-Phenoxyacridine (6·8 g.; Drozdov, *J. Gen. Chem. U.S.S.R.*, 1935, **5**, 1576), methylamine hydrochloride (2·5 g.), and phenol (30 g.) were heated for ½ hour at 120°, cooled, and treated with ether (50 ml.). The precipitate was dissolved in water (75 ml.) and treated with hydrochloric acid (5 ml.). The hydrochloride that separated on standing (85% yield) was collected and basified, giving *5-methylaminoacridine*, which was recrystallised quickly (to prevent hydrolysis) from 8 parts of 50% alcohol; canary-yellow crystals, m. p. 173—174° (sealed tube), somewhat soluble in water, soluble in 3·5 parts of alcohol without temperature gradient, and only moderately soluble in benzene or acetone (Found: C, 81·0; H, 6·0. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8%). The alcoholic solution has a greenish-blue fluorescence. The hydrochloride is the same shade of yellow as the base and is soluble in 2 parts of boiling and 10 parts of cold water. It shows no fluorescence by daylight, but ultra-violet light shows a green fluorescence that becomes bright violet on dilution. It is not affected by boiling with N-hydrochloric acid for an hour. *5-Dimethylaminoacridine hydrochloride*, similarly prepared from dimethylamine hydrochloride, was purified by dissolving in water (5 ml.) and adding acetone (100 ml.). After standing over-night, the hydrochloride was obtained in 75% yield as orange crystals, m. p. *ca.* 275° (decomp.). It is soluble in one part of water; the solution has no fluorescence by daylight and a blue-green one by ultra-violet light, but only when dilute (Found: N, 11·0. $C_{15}H_{14}N_2$,HCl requires N, 10·8%). When boiled with N/1-hydrochloric acid, it hydrolyses to acridone to the extent of 25% in an hour (5-aminoacridine is perfectly stable under these conditions), and sodium hydroxide acts similarly even in the cold. The base was therefore liberated from the salt with dimethylamine. It was yellow, and the alcoholic solutions did not fluoresce. Its general instability prevented its further examination.

Alkaline Hydrolyses.—The above two amines and 5-aminoacridine (0·1 g.) were separately boiled with potassium hydroxide (10 ml. of 5N, made up in 80% alcohol) and the evolved alkaline vapours were led into hydrochloric acid (25 ml. of N/50). The volume of boiling liquor was kept constant with alcohol, and after 2 hours the acid was back-titrated with N/50-alkali. The contents of the flask were then examined for 5-hydroxyacridine (acridone) which was found in quantities that tallied with the amounts of volatile bases titrated (see p. 460). When similarly treated, 1-, 2-, 3-, and 4-aminoacridines did not hydrolyse. When 5-aminoacridine was treated as above, but with omission of the potassium hydroxide, it still hydrolysed (1·25% per hour, observed over 8 hours). Catalysis is due here to hydroxyl ions derived from the base itself.

Acid Hydrolyses.—The amine (0·5 g.) was heated with concentrated hydrochloric acid (10 ml.) for 2 hours at 160—200° in a sealed tube (several such tubes of 1-aminoacridine exploded). Except in the case of the 5-isomeride, on cooling, the contents were distilled with sodium hydroxide, and the ammonia evolved was determined by titration. The flask residue was then filtered, the filtrate made faintly acid with acetic acid, and the precipitated hydroxyacridines dried and weighed, good correspondence with the ammonia values showing that diacridylamines were not formed; yields, 42, 70, 95, 98, and 10% of 1-, 2-, 3-, 4-, and 5-hydroxyacridines, respectively. 5-Hydroxyacridine was separated from unchanged 5-aminoacridine by extraction with dilute acetic acid in which the former is insoluble.

4-*Hydroxyacridine* was obtained in yellow needles from its blue solution in dilute alcohol, m. p. about 250° (decomp.) (Found: C, 79·5; H, 4·7; N, 7·35. $C_{13}H_9ON$ requires C, 80·0; H, 4·7; N, 7·2%). It gives a green solution in absolute alcohol and a yellow solution in benzene. The blue form is probably similar in constitution to 10-methylacrid-4-one (XIII) which is also blue (Nitzsche, *Angew. Chem.*, 1939, **52**, 517). The sodium salt gives a deep red, the hydrochloride a deep brown, aqueous solution without fluorescence. The m. p. of 2-hydroxyacridine, not previously recorded, was 285° (sealed, uncorr.). The other hydroxyacridines agreed with the properties given in the literature.

Anilinolyses.—The amine hydrochloride (1 g.) and aniline (10 ml.) were refluxed for 2 hours, sodium hydroxide (0·2 g.) added, the liquid steam-distilled, and the distillate extracted with ether. The phenylaminoacridines show little fluorescence either as bases or as salts. 1-*Phenylaminoacridine*, 75% yield, scarlet crystals from alcohol (orange solution), m. p. 187·5° (191° corr.), very soluble in benzene (Found: N, 10·4. $C_{19}H_{14}N_2$ requires N, 10·4%). Being a very weak base it is insoluble in dilute acetic acid, but gives a red solution in dilute hydrochloric acid. 2-*Phenylaminoacridine*, 45% yield, orange-yellow crystals from toluene, m. p. 231° (238° corr.) (Found: C, 84·4; H, 4·9; N, 10·4. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·4%). The scarlet hydrochloride was sparingly soluble in cold, more soluble in boiling, water. The acetate was soluble in cold water. 3-*Phenylaminoacridine*, 95% yield, yellow crystals from toluene, m. p. 229° (236° corr.) (Found: N, 10·5%). It gives a purple solution in dilute hydrochloric or acetic acids. 4-*Phenylaminoacridine*, 55% yield, red crystals with a blue glance, m. p. 220° (decomp.) (Found: N, 10·2%). It gives a pure blue solution in dilute acids and forms a blue sodium salt in alcoholic sodium hydroxide. 5-*Phenylaminoacridine*, 95% yield, orange-yellow crystals from alcohol, m. p. 224° (230·5° corr.) (Found: 84·1; H, 5·2; N, 10·5%). The hydrochloride is orange and sparingly soluble in water, the acetate is more soluble. 5-Aminoacridine *base* treated with aniline as shown gave only a 15% yield.

Hydrogenations.—These were carried out in the apparatus described by the authors (*Proc. Roy. Soc. N.S.W.*, 1941, **74**, 373). 1- and 2-Aminoacridanes agreed with the properties assigned to them by Clemo, Perkin, and Robinson (J., 1924, **125**, 1784) and Scherlin, Bras, Jakubowitsch, Worobjowa, and Ssergejew (*Annalen*, 1935, **516**, 218), respectively. The latter authors prepared 3-aminoacridane ("2-aminodihydroacridine" in their numbering) by the action of sodium on 3-nitroacridone. Their product is described as bright yellow, m. p. 191—192° (introduced at 190°), and soluble with a dark red colour in dilute hydrochloric acid; they analysed it only for nitrogen (14·34%). Our product consists of pale yellow plates from alcohol, m. p. 184—185° (sealed tube; 187—188° corr.), and soluble without colour in acids. The m. p. is independent of the temperature at which the specimen is introduced (Found: C, 79·4; H, 6·1; N, 14·1. 3-Aminoacridane, $C_{13}H_{13}N_3$, requires C, 79·5; H, 6·2; N, 14·28%. 3-Aminoacridine, $C_{13}H_{10}N_3$, requires C, 80·4; H,

5·2; N, 14·43%). When exposed to the air for a month, the surfaces of our crystals gave a red colour with hydrochloric acid and the m. p. of the sample had fallen to 180°. It would appear that the Russian authors' specimen was mainly 3-aminoacridine.

We wish to thank Professor J. C. Earl for many helpful suggestions, and Mrs. L. Buckley for the microanalyses.

UNIVERSITY OF SYDNEY. [*Received, October 13th*, 1942.]

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124. *Formation and Structure of Some Organic Molecular Compounds. Part II. Molecular Compounds of s-Trinitrobenzene with Some Unsaturated Ketones.*

By JOSEPH WEISS.

It is shown that a connection exists between the purely organic molecular compounds (cf. Part I; J., 1942, 245) and certain inorganic–organic molecular compounds. This has been demonstrated in the case of some ketones (dibenzylidene-, dicinnamylidene-, and di-*p*-anisylidene-acetone, etc.) in which the carbonyl group forms part of the conjugated system and which are known to form deeply coloured molecular compounds with strong acids on account of their basic properties. As this high proton affinity must be concurrent with the tendency to transfer electrons, these ketones should be capable of acting as donor molecules, *e.g.*, towards polynitro-compounds. Several new molecular compounds of these ketones with *s*-trinitrobenzene have been prepared, and their structure discussed.

THE organic molecular compounds are usually classified as purely organic (*e.g.*, those of polynitro-compounds, or quinhydrones) and as organic–inorganic, the latter being largely represented by the extensive group of the " oxonium salts " of alcohol, ethers, and ketones with strong acids and certain metal salts. It is the purpose of this communication to show that there exists a close link between the two classes, as now demonstrated in the case of certain (fully conjugated) ketones.

It is well known that many unsaturated ketones dissolve in concentrated sulphuric acid with a deep colour (cf. Hammett, " Physical Organic Chemistry," McGraw Hill, 1941). All these addition products with strong acids represent salts which are easily hydrolysed, their stability depending on the strength of the acid and the basicity of the ketone under consideration. Salt formation is appreciable in those cases where the ketone represents a system of fully conjugated double bonds. The addition of the proton then results in the formation of a positive ion with a resonance structure and with a non-localised charge (I); both are essential for the appearance of the deep colour actually observed (charge resonance spectra; cf. Mulliken, *J. Chem. Physics*, 1939, **7**, 570). The binding of the proton to the conjugated system of the ketone, with a certain localisation to the oxygen of the carbonyl group, involves, at least partly, the transfer of an electron from the carbonyl group to the proton. We may conclude, therefore, that, as with increasing basicity of the ketone the proton is more strongly bound, at the same time its tendency to give off an electron increases.*

$$\left[\begin{matrix}R\\R_1\end{matrix}\!\!>\!C\cdot OH\right]^+$$

(I.)

The basic properties of these ketones must therefore be co-existent with comparatively low ionisation potentials, and these ketones should be capable of acting as electron donors towards suitable acceptor molecules, which is an essential condition for the formation of molecular compounds (Part I, *loc. cit.*). We have found that some of these fully conjugated ketones are capable of forming stable molecular compounds with *s*-trinitrobenzene.

It was known that, *e.g.*, dibenzylideneacetone forms a molecular compound with picric acid (cf. Reddelien, *J. pr. Chem.*, 1915, **91**, 239), but as picric acid is itself a strong acid, the possibility exists—it is even highly probable—that it attaches itself by virtue of the proton of its hydroxyl group. Another small group of molecular compounds of ketones with *s*-trinitrobenzene is known (Sudborough, J., 1916, **109**, 1339), but in these ketones the carbonyl group does not form part of the conjugated system. The ketones are (with the one exception of distyryl diketone, for which, however, the only molecular compound reported has the ratio 1 ketone : 2 nitro-compound) all of the type $R\cdot CO\cdot CH_3$ (with R = α-naphthyl, phenyl-α-naphthyl, etc.), and the ability of these compounds to give molecular compounds is not due to the increase in " basicity " owing to the presence of the carbonyl group, as is clearly shown by the fact that the same group R (without the CO group) is equally capable of giving stable molecular compounds with *s*-trinitrobenzene.

This is quite different in the case of the ketones now studied (see table). Whereas molecular *compounds* are easily obtained from dibenzylidene-, benzylidene-*p*-anisylidene- di-*p*-anisylidene-, and dicinnamylidene-acetone, no molecular compound formation could be obtained with benzylidene-, *p*-anisylidene-, or cinnamylidene-acetone, which are all of the type $R\cdot CO\cdot CH_3$.

This also shows that, unlike the cases investigated by Sudborough, it is not the isolated hydrocarbon group (R) which is responsible for molecular compound formation, but the completely interlinked conjugated system, the link being provided by the carbonyl group. It is also known from absorption spectra of conjugated systems that the C=O double bond acts similarly to the (CH=CH) bond, *i.e.*, the π-electrons of oxygen act similarly to those of carbon (cf. Hausser, Kuhn, Smakula, and Deutsch, *Z. physikal. Chem.*, 1935, *B*, **29**, 378). This view is further supported by the molecular ratios as summarised in the table. If the two conjugated

* The conditions are similar to the case of ammonia and methylamine, where the stronger base methylamine has a greater proton affinity but lower ionisation potential as compared with ammonia (cf. Goeppert-Mayer and McCallum, *Rev. Mod. Physics*, 1942, **14**, 248).

Substance.	Relative basicity * (dibenzylidene-acetone = 1).	Molecular compound with *s*-trinitro-benzene.	Molecular ratio, ketone : *s*-trinitro-benzene.	M. p.
Benzylideneacetone	<1	(Not formed)	—	—
Dibenzylideneacetone	1	Light yellow	1 : 2	127°
		Light yellow	2 : 1	115
p-Anisylideneacetone	~1·5	(Not formed)	—	—
Benzylidene-*p*-anisylideneacetone	4·6	Yellow	1 : 1	114
		Yellow	1 : 2	124
Di-*p*-anisylideneacetone	6·0	Orange	1 : 1	115
		Orange	2 : 1	122
Cinnamylideneacetone	~1	(Not formed)	—	—
Dicinnamylideneacetone	4·2	Orange	1 : 1	113
		Yellow	1 : 2	110

* Measurements by Stobbe and Haertel (*Annalen*, 1909, **370**, 99), supplemented by author's measurements.

groups linked to the carbonyl group were to act independently, one should get a molecular ratio 1 ketone : 2 nitro-compound, whereas one also finds the ratio 1 : 1 or even 2 : 1.

The ionic structure of molecular compounds discussed in Part I represents a limiting case which has to be assumed, particularly in those cases where deep coloration accompanies molecular-compound formation and where the presence of ions or ion pairs is supported by other evidence. As mentioned in Part I (p. 246), the binding of the compounds may only be partly ionic, and other types of interactions may play their part under certain conditions.

A molecule of fully conjugated double bonds represents an electronic system similar to that of a metal (cf. London, *J. Physical Chem.*, 1942, **46**, 305); in general, the interaction between two such molecules could correspond to a sort of " alloy formation." As in the case of metals, if the two compounds are electronically very similar in their character we should expect only solid solutions to be formed, whereas if we have loosely bound electrons in the one component and an electron affinity in the other we should get molecular-compound formation corresponding to the intermetallic compounds in the case of metals.

Just as in the case of ordinary ionic compounds where the purely ionic character may partly disappear under certain (well-known) conditions, so the ionic molecular compounds with ions of high polarisability and great deformability of the electron clouds will show a partial redistribution of the electrons from the negative ion towards the positive ion. This amounts to a partial transfer of the electron, and in these cases the ionic compound is represented by the general formula $[A]^{\delta+}[B]^{\delta-}$ (where δ indicates as usual the fraction of the electronic charge). Molecular compounds of this type might show only a light colour not appreciably different from that of their components, and the molecular compounds discussed in this paper, for instance, belong to this group.

Experimental.—The preparation of the ketones followed the methods used by Baeyer and Villiger (*Ber.*, 1902, **35**, 1189; 1903, **36**, 2774; 1905, **38**, 582). The molecular compounds were prepared from the components in absolute alcohol and recrystallised from that solvent.

Dibenzylideneacetone–s-Trinitrobenzene.—1 : 2-*Compound*, m. p. 127° (Found: C, 52·7; H, 2·9; N, 11·9. $C_{17}H_{14}O,2C_6H_3O_6N_3$ requires C, 52·7; H, 3·0; N, 12·7%). 2 : 1-*Compound*, m. p. 115° (Found: C, 70·0; H, 4·3; N, 6·5. $2C_{17}H_{14}O,C_6H_3O_6N_3$ requires C, 70·45; H, 4·6; N, 6·2%).

Benzylidene-p-anisylideneacetone–s-Trinitrobenzene.—1 : 1-*Compound*, m. p. 114° (Found: C, 59·3; H, 4·2; N, 8·8. $C_{18}H_{16}O_2,C_6H_3O_6N_3$ requires C, 60·3; H, 4·0; N, 8·8%). 1 : 2-*Compound*, m. p. 124° (Found: C, 52·1; H, 3·2; N, 11·7. $C_{18}H_{16}O_2,2C_6H_3O_6N_3$ requires C, 52·1; H, 3·2; N, 12·15%).

Dianisylideneacetone–s-Trinitrobenzene.—1 : 1-*Compound*, m. p. 115° (Found: C, 59·3; H, 4·2; N, 8·8. $C_{19}H_{18}O_3,C_6H_3O_6N_3$ requires C, 59·2; H, 4·1; N, 8·3%). 2 : 1-*Compound*, m. p. 122° (Found: C, 65·5; H, 5·12; N, 5·3. $2C_{19}H_{18}O_3,C_6H_3O_6N_3$ requires C, 65·8; H, 4·9; N, 5·2%).

Dicinnamylideneacetone–s-Trinitrobenzene.—1 : 1-*Compound*, m. p. 113° (Found: C, 65·5; H, 4·2; N, 8·1. $C_{21}H_{18}O,C_6H_3O_6N_3$ requires C, 65·0; H, 4·2; N, 8·4%). 1 : 2-*Compound*, m. p. 110° (Found: C, 55·0; H, 3·3; N, 12·6. $C_{21}H_{18}O,2C_6H_3O_6N_3$ requires C, 55·7; H, 3·4; N, 11·8%).

The same procedure was adopted in the attempted preparation of the molecular compounds of benzylidene-, anisylidene-, and cinnamylidene-acetone, but no such compounds could be obtained even by varying the solvent or under different conditions.

My thanks are due to Professor Clemo, F.R.S., for his interest in this work.

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125. *The Oxygenation of Crotonaldehyde.*

By L. N. OWEN.

A quantitative study has been made of the absorption of oxygen by crotonaldehyde in the presence of various catalysts. In acetic acid solution, there is an optimum concentration of cobalt or manganese at which oxygenation is most efficient, but copper is ineffective at any concentration. In the absence of a solvent, cobalt and manganese are detrimental, whereas copper again has little effect. Increased temperature is also to be avoided. Crotonic acid is obtained in highest yield by the use of pure crotonaldehyde in the absence of any catalyst, precautions being taken against undue rise in temperature. Side reactions, involving attack at the double bond, lead to the formation of *dl-erythro-*$\alpha\beta$-dihydroxybutyric acid, which has been isolated as one

of the by-products. The synthesis of *crotyl crotonate*, and the formation of a calcium chloride *compound* of crotonaldehyde, $CaCl_2,2C_4H_6O$, are described.

THE difficulty of obtaining a high yield of crotonic acid by treatment of crotonaldehyde with air or oxygen is well known (Duchesne and Delépine, *Bull. Soc. chim.*, 1924, **35**, 1311; Rupe and Schaerer, *Helv. Chim. Acta*, 1925, **8**, 853; Kaufler and Halbig, *Monatsh.*, 1929, **53—54**, 119). According to B.P. 165,728, oxygenation of crotonaldehyde in acetic acid containing 0·1—0·2% of manganese (as manganic acetate) leads to formation of crotonic acid in 98—99% yield; this is presumably calculated on a "weight for weight" basis, and corresponds to a yield of 80% of the theoretical. Duchesne and Delépine (*loc. cit.*) could not confirm this claim, and the present work has demonstrated that a catalyst concentration of 0·1% is not the most effective.

FIG. 1.

Oxygenation of crotonaldehyde in acetic acid at 20° with manganese catalyst.

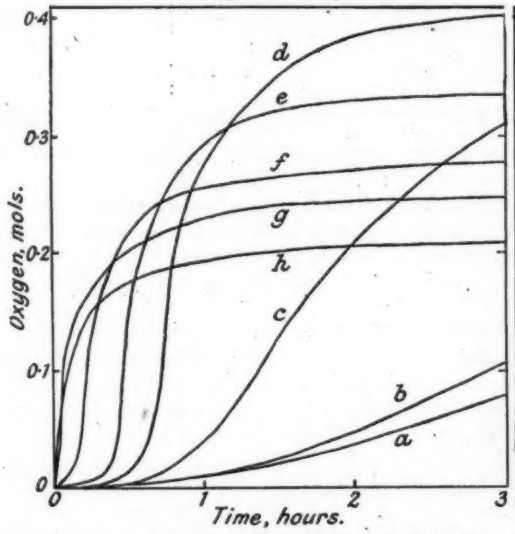
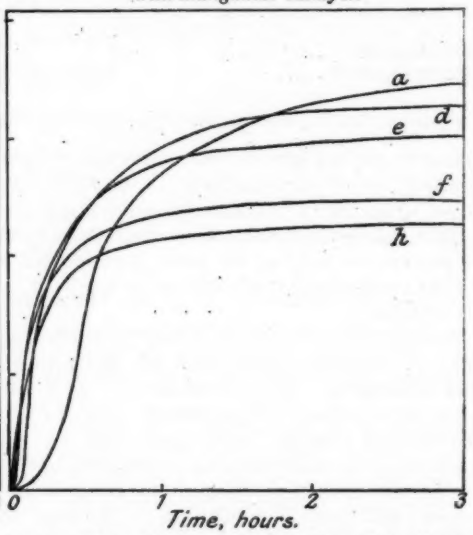


FIG. 2.

Oxygenation of crotonaldehyde in acetic acid at 40° with manganese catalyst.

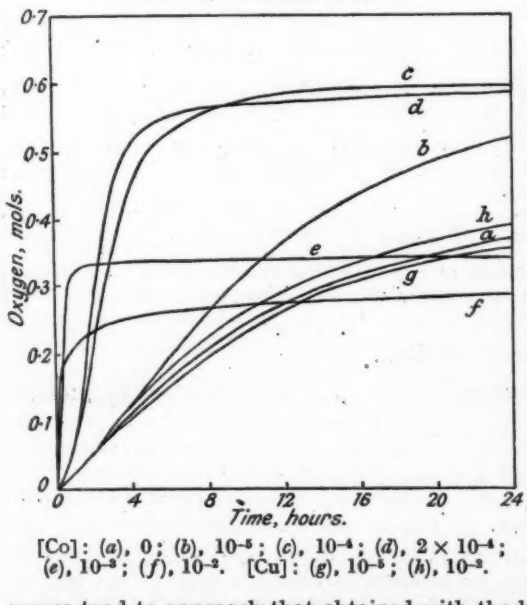


[Mn]: (*a*), 0; (*b*), 2×10^{-7}; (*c*), 6×10^{-7}; (*d*), 2×10^{-6}; (*e*), 4×10^{-6}; (*f*), 2×10^{-5}; (*g*), 2×10^{-4}; (*h*), 4×10^{-3}.

Dry crotonaldehyde, dissolved in an equal volume of acetic acid containing known amounts of manganic acetate, was shaken in oxygen at room temperature, the absorption of gas being measured. With a catalyst concentration of 4×10^{-3} mol./l. (*i.e.*, *ca.* 0·1%), absorption was rapid at first but ceased when about half the theoretical amount of oxygen had been acquired. On progressive reduction of the catalyst concentration to 2×10^{-6} mol./l., there was a remarkable increase in the oxygen absorption, but further reduction in concentration resulted in a diminution in the rate of reaction. The optimum value of about 2×10^{-6} mol./l. thus brought about the maximum absorption of oxygen in a reasonable time (about 3 hours). The curves (Fig. 1) show, as would be expected, that the induction period increases as the catalyst concentration is diminished, but it is not clear why the higher concentrations eventually inhibit the oxidation. A high rate of destruction of per-acid by the catalyst would probably bring about such a result, but the reaction products, except those from the use of the highest catalyst concentration, always showed the presence of peroxide or per-acid.

FIG. 3.

Oxygenation of crotonaldehyde in acetic acid at 20° with cobalt or copper catalyst.



[Co]: (*a*), 0; (*b*), 10^{-5}; (*c*), 10^{-4}; (*d*), 2×10^{-4}; (*e*), 10^{-3}; (*f*), 10^{-2}. [Cu]: (*g*), 10^{-5}; (*h*), 10^{-2}.

At 40°, the deleterious effect of manganese was still noticeable (Fig. 2), but with rise in temperature the curves tend to approach that obtained with the highest catalyst concentration, a curve which itself is almost independent of temperature [compare Fig. 1(*h*) and Fig. 2(*h*)]. Indeed, at 60° the catalyst concentration had little effect on either the rate or the extent of the reaction, all the curves obtained being practically identical with (*h*), Fig. 2.

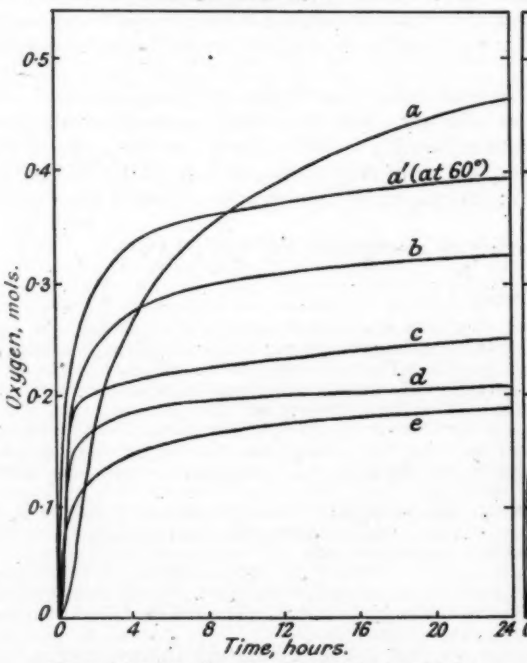
Further experiments, carried out at room temperature only, indicated that there was a similar sensitivity to catalyst concentration when cobalt acetate was used. Copper acetate, on the other hand, was without appreciable effect at any concentration (Fig. 3).

In the absence of solvent, the presence of manganese was detrimental at all concentrations, oxidation being most efficient when no catalyst was used (Fig. 4), crotonic acid then crystallising out during the course of the oxidation. With cobalt, higher concentrations behaved in a similar manner; lower concentrations, although accelerating the initial absorption of oxygen, did not result in a yield of crotonic acid better than that obtained without a catalyst (Fig. 5). The presence of copper in various amounts did not greatly affect the course of the oxidation or the yield of acid.

Treatment of pure crotonaldehyde with oxygen under a pressure of 5 atm. resulted in an earlier separation of solid crotonic acid, and by fractional distillation of the products it was obtained in 70% yield. When the experiment was repeated on a larger scale, the heat of reaction caused a considerable rise in temperature, the product remained liquid, and the yield of crotonic acid was only 27%. The importance of temperature control was also shown by an experiment at ordinary pressure at 60°, in which the oxygen absorption was rapid at

FIG. 4.

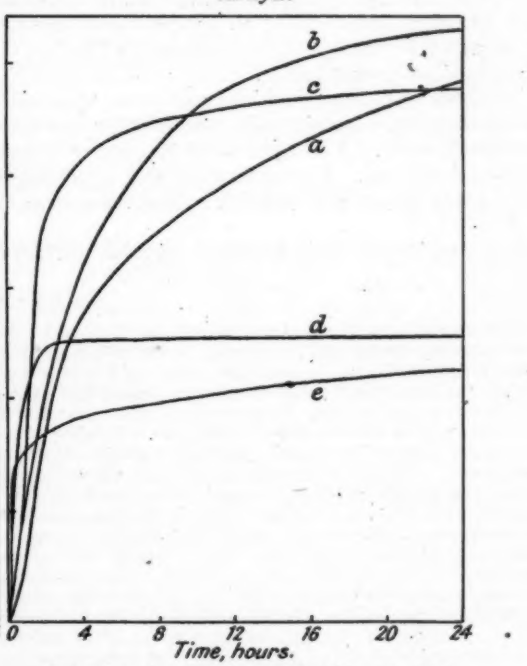
Oxygenation of crotonaldehyde at 20° with manganese catalyst.



[Mn]: (*a*), 0; (*b*), 2×10^{-6}; (*c*), 4×10^{-6}; (*d*), 2×10^{-4}; (*e*), 4×10^{-4}.

FIG. 5.

Oxygenation of crotonaldehyde at 20° with cobalt catalyst.



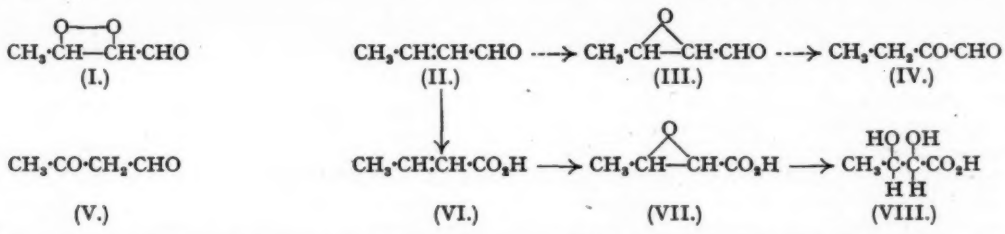
[Co]: (*a*), 0; (*b*), 4×10^{-6}; (*c*), 4×10^{-5}; (*d*), 4×10^{-4}; (*e*), 4×10^{-3}.

first, but was finally less than that attained in the cold [Fig. 4(*a'*)]; furthermore, no solid separated, and a smaller amount of acid was isolated on distillation.

The highest yield of crotonic acid is therefore produced by the simple procedure of oxygenating pure crotonaldehyde, with precautions against undue rise in temperature. Even so, however, the yield is less than that calculated from the volume of oxygen absorbed, an observation which applies indeed to all the experiments, including those in acetic acid, and suggests that some side reaction occurs, probably involving the ethylenic linkage. Duchesne and Delépine (*loc. cit.*) postulated the formation of the peroxide (I), followed by breakdown to acetic acid, which they identified as one of the products, and a fragment "CH·CHO" which would presumably appear as glyoxal or one of its oxidation products; Young (*J. Amer. Chem. Soc.*, 1932, **54**, 2498) also claimed to have isolated acetic acid, but the yield and mode of identification were not recorded. It has now been shown that during the oxidation there is a diminution in unsaturation value, thus confirming that the double bond is attacked, and efforts have been made to identify the reaction products.

Distillation in steam removed crotonic acid and unchanged crotonaldehyde, and from later portions of the distillate there was obtained a *bis*-2 : 4-*dinitrophenylhydrazone*, $C_{16}H_{14}O_8N_8$, m. p. 298°. With warm aqueous or cold alcoholic alkali it gave the intense violet colour typical of a dinitrophenylosazone, which suggested that it was the derivative of ethylglyoxal (IV), possibly formed from crotonaldehyde (II) *via* the glycidic aldehyde (III). Ethylglyoxal-2 : 4-dinitrophenylosazone was prepared; it had m. p. 247°, as stated by Ingold, Pritchard, and Smith (J., 1934, 79), and behaved similarly. The isomeric derivative from diacetyl had m. p. 335° (Mat-

thiessen and Hagedorn, *Mikrochem.*, 1941, **29**, 55) and gave the colour only with alcoholic alkali. An alternative, though highly improbable, isomerisation of (III) would yield acetoacetaldehyde (V), which in the acid medium



would be rapidly converted into 1 : 3 : 5-triacetylbenzene (Claisen and Stylos, *Ber*, 1888, **21**, 1144). The substance of m. p. 298° cannot therefore be derived from (V), and it is suggested that it may be a stereoisomer of the ethylglyoxal osazone.

The portion non-volatile in steam yielded crystalline *dl-erythro*-αβ-dihydroxybutyric acid (VIII), from which the p-*phenylphenacyl* ester was prepared. This acid is obtained by the action of water on β-methylglycidic acid (VII), which is readily formed from crotonic acid (VI) in the presence of per-acids (Braun, *J. Amer. Chem. Soc.*, 1929, **51**, 228; 1930, **52**, 3185). Such oxidising agents are usually produced during the autoxidation of aldehydes, and this mechanism is supported by the fact that the reaction products liberated iodine from an acidified solution of potassium iodide.

Analysis of a reaction mixture gave an appreciable ester value, but in view of the presence of unchanged crotonaldehyde, which is easily resinified by treatment with hot alkali, it is doubtful whether this observation is of much value. A distinct ester-like odour was noticeable with some fractions, but the cause of this could not be ascertained. The absence of any appreciable quantity of *crotyl crotonate* was established by synthesis of this ester from crotyl bromide and silver crotonate: its properties were entirely different from those of any fraction.

Crotonaldehyde was found to form with calcium chloride a *compound*, $CaCl_2,2C_4H_6O$.

Experimental.

Crotonaldehyde (A. Boake, Roberts and Co., Ltd.) was dried over calcium chloride and redistilled, the fraction of b. p. 103—105° being used. Oxygen was stored over water in a graduated cylinder, connected through a sulphuric acid drying bottle to the 10-c.c. reaction vessel, attached to a shaking machine and fitted with a small electric heater for work at higher temperatures. The heater was controlled by a variable resistance in series with an ammeter, which had been calibrated by preliminary experiments so that at a fixed rate of shaking (300 r.p.m.) the contents of the vessel could be maintained at any desired temperature. In view of the great effect produced by slight traces of catalysts, particular care was necessary to ensure that the reaction vessel and its connecting tubes were thoroughly cleaned before each experiment. After introduction of the material to be oxidised, air was replaced by oxygen, any necessary adjustments of temperature made, and the shaker set in operation at 300 r.p.m.

Catalyst Solutions.—A stock solution of manganese acetate was prepared by a slight modification of B.P. 165,728: To manganese acetate (1 g.), dissolved in boiling acetic acid (50 c.c.), was added a solution of potassium permanganate (0·15 g.) in hot water (5 c.c.). After cooling, the volume was made up to 500 c.c. with acetic acid, the catalyst concentration thus being 0·2%, calculated as manganese acetate, *i.e.*, 8×10^{-3} mol./l. Stock solutions of cobalt and copper acetates, each containing 2×10^{-2} mol./l., were made by dissolving the solids in acetic acid. Other concentrations were prepared by progressive dilution with acetic acid of portions of the stock solutions. The catalyst concentrations given in Figs. 1—5 refer to the net concentrations in the reaction mixtures employed.

Oxygenations in Acetic Acid.—(A) *With manganese catalyst* (see Figs. 1 and 2). The experiments were carried out in each instance on dry crotonaldehyde (3·5 c.c.) mixed with the catalyst solution (3·5 c.c.). With the higher concentrations there was an appreciable rise in temperature during the early stages of the reaction, but on repetition with a cooling bath surrounding the vessel there was little alteration in the ultimate absorption of oxygen, *e.g.*, 0·21 mol. after 2 hours with a catalyst concentration of 4×10^{-3} mol./l. [cf. curve (*h*), Fig. 1]. At 60°, with [Mn] ranging from 0 to 4×10^{-3}, all oxygenations took the same course, approximately that of curve (*h*), Fig. 2.

With the exception of the experiment in which the concentration was 4×10^{-3} mol./l., the reaction mixtures obtained by oxygenation at room temperature contained appreciable amounts of per-acid or peroxide (see above). In some instances, the total acidity of the final reaction mixture was determined by titration with standard alkali. The increased acidity was always less than that calculated on the basis of oxygen absorption, *e.g.*, the product from (*h*), Fig. 1 (Found: crotonic acid, 1·05 g. Calc.: 1·54 g.), and from (*d*), Fig. 1 (Found: 1·76 g. Calc.: 2·95 g.).

Examination of oxidation products. The combined products from a number of experiments at 20° were steam-distilled. Acetic acid, crotonic acid, and unchanged crotonaldehyde distilled first, and from later portions 2 : 4-dinitrophenylhydrazine sulphate afforded in small yield a *bis*-2 : 4-*dinitrophenylhydrazone*, forming orange-red needles, m. p. 298° (Found: C, 42·7; H, 3·1; N, 25·1. $C_{16}H_{14}O_8N_8$ requires C, 43·0; H, 3·2; N, 25·1%), from nitrobenzene; its properties are discussed above.

The aqueous residue from the steam distillation was neutralised with barium carbonate, filtered from some tarry impurities, and evaporated to small bulk. The barium salts were precipitated with alcohol, filtered off, and dried in a vacuum. The powdered product (30 g.) was added to 8% methyl-alcoholic hydrogen chloride (200 c.c.), and after a few hours the precipitated barium chloride was filtered off. The solution, which now contained about 3% of hydrogen chloride, was refluxed for 9 hours, cooled, neutralised with silver carbonate, and filtered. The esters obtained on removal of the solvent were fractionated under 15 mm. to give: (i), 0·40 g., b. p. 55—85°, $n_D^{20°}$ 1·3840; (ii), 0·85 g., b. p. 85—120°, $n_D^{20°}$ 1·4288; (iii), 1·45 g., b. p. 120—122°, $n_D^{20°}$ 1·4492. Fraction (iii) was methyl *dl-erythro-αβ*-dihydroxybutyrate (Found: OMe, 22·9; equiv., 132. Calc. for $C_5H_{10}O_4$: OMe, 23·2%; equiv., 134). It was heated on the water-bath for 2 hours with excess of baryta, cooled, and treated with a slight deficiency of sulphuric acid. The filtered solution was evaporated under reduced pressure, and the residue extracted with hot ethyl acetate. Removal of the solvent gave a syrup from

which crystals of *dl-erythro-αβ*-dihydroxybutyric acid slowly separated. These were triturated with ether and recrystallised from ethyl acetate, forming needles, m. p. and mixed m. p. 81° (Found: equiv., 121. Calc.: 120). The *p-phenylphenacyl* ester crystallised from methyl alcohol in rosettes of needles, m. p. 130° (Found: C, 68·6; H, 6·2. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%).

(B) *With cobalt and copper catalysts.* The results shown in Fig. 3 were obtained with mixtures of crotonaldehyde (3·0 c.c.) and the catalyst solution (3·0 c.c.) of appropriate concentration. A further quantity of the above osazone, m. p. 297° from acetic anhydride, was isolated after steam distillation of the products (Found: C, 42·5; H, 3·0%).

Oxygenations without Solvent.—To dry crotonaldehyde (5·0 c.c.) was added a catalyst solution (0·1 c.c.) of concentration 50 times that required for the experiment.

(A) *With manganese catalyst* [see Fig. 4, (*b*), (*c*), (*d*), and (*e*)]. All reaction mixtures remained liquid.

(B) *With cobalt catalyst* (see Fig. 5). The heat developed in the first few minutes of experiments (*d*) and (*e*) was sufficient momentarily to cause the liquid to boil; only in the other experiments did crystalline crotonic acid separate during the oxidation. Repetition of (*d*) and (*e*), with a cooling-bath surrounding the vessel, resulted in a slower rate of reaction, but the final uptake of oxygen was hardly affected, being 0·27 and 0·24 mol. respectively, proportions which are almost identical with those shown in Fig. 5.

(C) *With copper catalyst.* [Cu] was varied from 0 to 5 × 10^{-3}, but the course of the reaction was unaffected. Solid crotonic acid separated during each oxidation, and the yield obtained on distillation was approximately the same as in the absence of a catalyst (see below).

(D) *No catalyst.* Dry crotonaldehyde (5·0 c.c.) was used. Crotonic acid began to separate after about 8 hours. The curve (*a*) showing the course of the oxidation is included in Figs. 4 and 5. Distillation of the product at 60 mm. gave: (i), 0·8 g., b. p. 45—110°; (ii), 3·1 g., b. p. 110—112°, crystallising as crotonic acid; (iii), 0·4 g., residue. A further quantity of crotonic acid, estimated by titration to be 0·5 g., was present in fraction (i).

The oxidation was repeated, and the semi-solid reaction product diluted to 100 c.c. with water. Titration with alkali indicated an acid content equivalent to 4·1 g. of crotonic acid. The apparent ester value corresponded to a further 0·4 g. of crotonic acid, and the unsaturation value to 4·5 g. of crotonic acid or 3·7 g. of crotonaldehyde. There had been, therefore, a diminution in the unsaturation value (since the amount of crotonaldehyde originally present was 4·3 g.), indicating some side reactions involving the double bond. The solution liberated iodine from acidified potassium iodide, but equivalent to a content of only 0·04 g. of percrotonic acid. The remainder of the aqueous solution was steam-distilled, and again there was isolated a bis-2:4-dinitrophenylhydrazone, m. p. 295° (Found: C, 42·6; H, 3·3%). The non-volatile portion contained a trace of oxalic acid, identified by formation of its calcium salt.

An oxidation at 60° [curve (*a'*), Fig. 4] gave a liquid product which on distillation at 60 mm. yielded: (i), 2·1 g., b. p. 45—110°; (ii), 2·0 g., b. p. 110—113°, crystallising as crotonic acid; (iii), 0·7 g., residue. The total crotonic acid was estimated to be 2·7 g.

Oxidation under pressure. Dry crotonaldehyde (10 c.c.) was oxidised in a thick-walled glass bottle fitted to a shaking machine and connected by pressure tubing to a small reservoir containing oxygen under a pressure of about 5 atm. A pressure gauge on the reservoir gave a rough indication of the rate of absorption of oxygen, but no quantitative measurements were made. The rate was greater than at ordinary pressure, and solid crotonic acid separated after 4 hours, but the reaction was allowed to proceed for 24 hours to ensure the maximum yield. The products from 5 such experiments were combined, and solid crotonic acid (6·5 g.) filtered off (much of it had been unavoidably dissolved in transference from the reaction vessel). Fractionation under 60 mm. then gave: (i), 9·0 g., b. p. 45—110°; (ii), 30·5 g., b. p. 110—112°, crystallising as crotonic acid; (iii), 4·0 g., residue. The yield of crotonic acid was thus 37·0 g., *i.e.*, 70% of the theoretical. It is probable that fraction (i) also contained an appreciable amount.

When the oxidation under pressure was repeated on a larger amount (50 c.c.) of crotonaldehyde, the heat of reaction caused a pronounced rise in temperature and a yellow colour developed. After 24 hours, the product, from which no solid had separated, was fractionated. The crotonic acid amounted to only 14 g., *i.e.*, 27%.

Preparation of Crotyl Crotonate.—Crotyl alcohol, b. p. 119—121°, $n_D^{17°}$ 1·4290, was prepared by the method of Young, Hartung and Crossley (*J. Amer. Chem. Soc.*, 1936, **58**, 100). From light petroleum (b. p. 60—80°), the phenylurethane crystallised in colourless needles, m. p. 79° (Verhulst, *Bull. Soc. chim. Belg.*, 1931, **40**, 85, gives m. p. 80°; Newman and Rydon, J., 1936, 261, give m. p. 65°), and the α-naphthylurethane in needles, m. p. 96—97° (Hess and Wustrow, *Annalen*, 1924, **437**, 256, give m. p. 89°). The 3:5-*dinitrophenylurethane*, prepared by heating the alcohol (0·2 g.) with 3:5-dinitrobenzazide (0·6 g.) in toluene (3 c.c.) at 100° for 1 hour (see Smith and Sprung, *J. Amer. Chem. Soc.*, 1942, **64**, 433), crystallised from toluene in plates, m. p. 106—108° (Found: C, 47·6; H, 4·0; N, 14·5. $C_{11}H_{11}O_6N_3$ requires C, 47·1; H, 4·0; N, 15·0%).

Crotyl bromide was prepared from the alcohol (4·5 g.) by addition of hydrobromic acid (15 c.c., *d* 1·7). There was an immediate separation of a dark oil, and after 4 hours at room temperature this was removed, washed with water, sodium carbonate solution, again with water, dried over calcium chloride, and distilled: (i), 1·5 g., b. p. 100—105°, $n_D^{23°}$ 1·4745; (ii), 4·8 g., b. p. 105—110°, $n_D^{23°}$ 1·4760. Fraction (ii), which distilled with a constant refractive index, was used for the following esterification.

To finely powdered silver crotonate (8 g.), suspended in dry ether (40 c.c.), was added crotyl bromide (4·8 g.). Reaction was vigorous, causing the ether to boil gently, and after standing for 2 hours the silver bromide was filtered off. Removal of ether from the filtrate gave an oil which was distilled under 60 mm.: (i), 1·0 g., b. p. 95—100°, $n_D^{25°}$ 1·4400; (ii), 2·4 g., b. p. 100—105°, $n_D^{25°}$ 1·4450; (iii), 1·0 g., b. p. 105—107°, $n_D^{25°}$ 1·4490. Fraction (ii), an oil with a pleasant odour, had b. p. *ca.* 175°/770 mm. (Found: C, 67·6; H, 8·5; equiv., 137; $|\overline{\overline{1\cdot67}}$. $C_8H_{12}O_2$ requires C, 68·5; H, 8·6%; equiv., 140; $|\overline{\overline{2\cdot0}}$). This *crotyl crotonate* was probably contaminated with a small proportion of methylvinylcarbinyl crotonate (α-methylallyl crotonate), for Winstein and Young (*J. Amer. Chem. Soc.*, 1936, **58**, 104) have shown that crotyl bromide, as usually prepared, is in equilibrium with *ca.* 15% of methylvinylcarbinyl bromide.

Search for Crotyl Crotonate in the Oxidation Products.—From the b. p. of the synthetic ester it was evident that it might have been present either in admixture with the crystalline crotonic acid distillates or in the preceding fraction, usually collected at 45—110°/60 mm. A quantity of the latter material, collected from several oxidations, was dissolved in ether and shaken with aqueous sodium carbonate to remove traces of acid. The ethereal layer was dried and evaporated to an oil (6 g.) from which, on distillation, however, crotyl crotonate could not be isolated.

The solid crotonic acid distillates often had an ester-like odour. Some of this material (48 g.) was crystallised once from water to give pure crotonic acid, m. p. 72°. The mother-liquors were basified with sodium carbonate solution and extracted with ether. Evaporation of the dried extract gave an oil (0·5 g.) which was distilled: (i), 0·2 g., b. p. 120—170°, $n_D^{20°}$ 1·4325; (ii), 0·2 g., b. p. 170—180°, $n_D^{20°}$ 1·4460. Both fractions had negligible ester values and gave oily products with aqueous 2:4-dinitrophenylhydrazine sulphate.

Calcium Chloride Compound of Crotonaldehyde.—Finely powdered anhydrous calcium chloride (7 g.) was shaken in a stoppered bottle with an excess (17 g.) of dry crotonaldehyde. After standing overnight, the pasty mass was shaken with dry ether (50 c.c.), rapidly filtered off, washed with more dry ether (50 c.c.), transferred to a vacuum desiccator, and kept under reduced pressure until no further loss in weight occurred. The *compound* so obtained (Found: Cl, 28·6;

loss on heating, 55·1; $|\overline{\text{Ign}}$. $CaCl_2,2C_4H_6O$ requires Cl, 28·3; loss, 55·8%; $|\overline{\text{Ign}}$) slowly decomposed in moist air with evolution of crotonaldehyde. On heating, it left a residue of calcium chloride.

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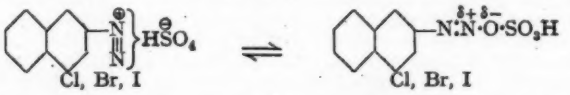
126.—*Preparation of 4-Halogeno-2-naphthols and 4-Nitro-2-naphthol, with a Note on the Resonance Structure of the Internal Diazo-oxides (Diazo-naphthols).*

By HERBERT H. HODGSON and STANLEY BIRTWELL.

4-Chloro-, 4-bromo-, and *4-iodo-2-naphthols* are prepared from the corresponding 4-halogenonaphthalene-1 : 2-diazo-oxides (diazo-naphthols). A method is described for the rapid preparation of 4-nitro-2-naphthol. The properties of the diazo-naphthols indicate them to be resonance hybrids.

FAILURE to obtain the 4-halogeno-2-naphthols in satisfactory quantity from the corresponding 4-halogeno-2-naphthylamines by customary methods has revealed a noteworthy difference between the decompositions of the diazonium sulphates of 4-halogeno-2-naphthylamines and the 3-halogenoanilines in boiling aqueous sulphuric acid : the latter give almost quantitative yields of the 3-halogenophenols (Hodgson, E.P. 200,714), but the former yield only traces of the 4-halogeno-2-naphthols, the product being almost entirely 4′-halogenonaphthalene-2′ : 1-azo-4-halogeno-2-naphthol, owing to coupling of the 4-halogeno-2-naphthol with still undecomposed diazonium sulphate. Since only traces of naphthol can be isolated, the velocity of coupling must be at least equal to that of decomposition, and indicates that the 4-halogenonaphthalene-2-diazonium sulphates are not only very stable towards boiling sulphuric acid but possess high coupling power. The latter property points to a predominance of the diazo-component (right-hand side) in the equilibrium mixture, since it is only the diazo-component that can couple (cf. Schoutissen, *J. Amer. Chem. Soc.*, 1933, **55**, 4541) :



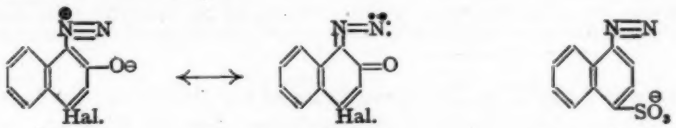
Attempts to prepare 4-halogeno-2-naphthols by treatment of 4-halogeno-2-naphthylamines with sodium bisulphite, acetone bisulphite, and sodium bisulphite and sulphur dioxide failed, and heating the 4-halogeno-2-naphthylamine with 20% hydrochloric acid under pressure (Bucherer's reaction, *J. pr. Chem.*, 1904, **69**, 49) afforded traces only of 4-halogeno-2-naphthol after 24 hours. 4-Amino-2-naphthol, prepared with difficulty (cf. Morgan and Evens, J., 1919, **115**, 1126), proved so susceptible to oxidation that manipulation was only possible in an atmosphere of carbon dioxide; the improvement effected by Ingold (J., 1923, **123**, 2066) *via* 4-nitro-2-naphthyl toluene-*p*-sulphonate involved recourse to such reducing agents as amalgamated aluminium foil in moist ether, which were obviously unsuitable for large-scale operations. Finally, the method of Morgan and Evens (*loc. cit.*), who obtained 4-nitro-2-naphthol in 58—64% yield by boiling 4-nitronaphthalene-1 : 2-diazo-oxide for 32 hours with aluminium powder and alcohol, was found to be capable of general application. 4-Chloro- and 4-bromo-naphthalene-1 : 2-diazo-oxides required 18—20 hours' boiling for complete decomposition (no further coupling with alcoholic alkaline resorcinol), the iodo-analogue only 4 hours, and naphthalene-1 : 2-diazo-oxide-4-sulphonic acid did not require aluminium powder for its decomposition (Ingold, *loc. cit.*). Shorter periods of boiling (*e.g.*, 5 hours) afforded satisfactory yields (41%) (cf. Ingold, *loc. cit.*). The tedious extraction of the naphthol with boiling water; as prescribed by Morgan and Evens (*loc. cit.*) for the isolation of 4-nitro-2-naphthol, was replaced by extraction with cold 2% aqueous sodium hydroxide (so dilute because of the sparing solubility of the sodium salts of the 4-halogeno-2-naphthols), whereby the small amount of by-product, 4 : 4′-dihalogeno-1 : 1′-azonaphthol was also extracted, as shown by the bright red colour of the solution. The latter compound was removed as a barium lake by treatment of the alkaline extract with barium chloride.

Decomposition of 4-nitronaphthalene-1 : 2-diazo-oxide by boiling alcohol and metallic copper, generated *in situ* by the action of iron filings on copper sulphate, gave a 50% yield of 4-nitro-2-naphthol in 30 minutes : this is the most convenient method for its preparation in quantity (the yield is only 38% in 12 hours when ordinary copper is used; Morgan and Evens, *loc. cit.*).

4-Chloro- and 4-bromo-naphthalene-1 : 2-diazo-oxides were decomposed more rapidly by sodium stannite, but the yields were variable and the products of inferior quality.

The Resonance Structure of the Internal Diazo-Oxides.—The difficulty of replacement of the diazo-nitrogen by hydrogen in the above diazo-naphthols is in the order of the negative inductive (–*I*) effects of their *p*-substituents, *viz.*, $NO_2 > Cl > Br > I > SO_3H$; *i.e.*, the diazo-oxide group is stabilised by the *p*-substituents in this order. Such uniformity of replacement suggests that the diazo-naphthols contain a diazonium group (I*a*), analogous cases being the diazonium sulphates and the diazo-aryl sulphonates (Saunders, " The Aromatic Diazo-Compounds," pp. 32, 39). This structure is in harmony with the solubilities of the diazo-naphthols in

hot water and sparing solubilities in non-polar solvents such as light petroleum, and with their decomposition (sometimes with explosive violence) on fusion; on the other hand, their pronounced colours indicate ease of transition to a quinonoid structure (I*b*). The existence of both structures is reconciled by formulation of the diazo-naphthols as resonance hybrids (I); since only the positions of the electrons are involved in the two forms, the resonance energy would account for the stability, and the betaine (zwitter-ion) structure for the diazonium form is established for such analogous compounds as the slightly soluble and explosive diazonium sulphonates, *e.g.*, diazonaphthionic acid (II) (cf. Sidgwick, " Organic Chemistry of Nitrogen," revised by Taylor and Baker, Oxford, 1937, p. 422):



(I*a*.) (I*b*.) (II.)

Experimental.

Decomposition of 4-Halogenonaphthalene-1 : 2-diazo-oxides by Alcohol and Aluminium Powder.—*4-Chloro-2-naphthol* was obtained when 4-chloronaphthalene-1 : 2-diazo-oxide (2·0 g.) (Hodgson and Birtwell, this vol., p. 322) was boiled for 19 hours with ethyl alcohol (50 c.c.) and aluminium powder (0·75 g.), until the mixture no longer gave a blue or purple colour with alkaline resorcinol. The aluminium powder was removed by filtration and the alcohol by distillation, the tarry residue extracted with cold 2% aqueous sodium hydroxide (20 c.c.), the filtered extract diluted with an equal volume of water, and a solution of crystallised barium chloride (1·2 g.) in water (20 c.c.) added; the solution, after being heated almost to boiling, was filtered at room temperature and diluted with ice, and hydrochloric acid added to precipitate the 4-chloro-2-naphthol (1·5 g.; 84·3% yield), which crystallised from 30% aqueous alcohol (charcoal) in colourless feathery needles, m. p. 100° (Found: Cl, 19·8. $C_{10}H_7OCl$ requires Cl, 19·9%). The sodium salt was sparingly soluble in cold 10% aqueous sodium hydroxide.

4-Chloro-1-benzeneazo-2-naphthol, prepared from diazotised aniline and alkaline 4-chloro-2-naphthol, crystallised slowly from acetone in orange-red needles, m. p. 165° (Found: Cl, 12·5. $C_{16}H_{11}ON_2Cl$ requires 12·6%), and from chlorobenzene in crimson needles, which changed on keeping in air to the orange-red variety. The latter after fusion and solidification had m. p. 151°, but resolidified at *ca.* 155°, and remelted at 165° if the temperature was allowed to rise very slowly; the process could be repeated.

4-Chloro-2-naphthyl methyl ether, prepared from 4-chloro-2-naphthol, aqueous sodium hydroxide, and methyl sulphate, crystallised from light petroleum (charcoal) in colourless plates, m. p. 44—45° (Found: Cl, 18·3. $C_{11}H_9OCl$ requires Cl, 18·4%).

4-Chloro-2-naphthyl acetate, obtained by refluxing 4-chloro-2-naphthol with excess of acetic anhydride for 30 minutes (90—100% yield), crystallised from aqueous methyl alcohol in colourless plates, m. p. 56° (Found: Cl, 16·0. $C_{12}H_9O_2Cl$ requires Cl, 16·1%).

4-Bromo-2-naphthol, obtained by the method used for the chloro-analogue (77% yield), crystallised from aqueous methyl or ethyl alcohol (charcoal) in colourless feathery needles, m. p. 122° (Fries and Schimmelschmidt, *Annalen*, 1930, **484**, 245, give m. p. 122°) (Found: Br, 35·7. Calc.: Br, 35·8%).

4-Bromo-1-benzeneazo-2-naphthol crystallised from glacial acetic acid in bright red needles, m. p. 160° (Found: Br, 24·3. $C_{16}H_{11}ON_2Br$ requires Br, 24·4%), *4-bromo-2-naphthyl methyl ether* from light petroleum in light colourless plates (flat parallelepipeds), m. p. 64° (Found: Br, 33·6. $C_{11}H_9OBr$ requires Br, 33·7%), and *4-bromo-2-naphthyl acetate* from aqueous methyl alcohol (charcoal) in colourless plates, m. p. 61° (Found: Br, 30·1. $C_{12}H_9O_2Br$ requires Br, 30·2%).

Reduction of 4-Chloro- and 4-Bromo-naphthalene-1 : 2-diazo-oxide by Sodium Stannite.—The diazo-oxide (prepared from 0·1 g.-mol. of the 4-halogeno-2-nitro-1-naphthylamine) was made into a slurry with warm water (220 c.c.) and added during 20 minutes to a solution of stannous chloride crystals (40 g.) in 10% aqueous sodium hydroxide (400 c.c.) maintained at 80—90°. The mixture was heated for another 10 minutes, nitrogen being evolved, and the deep purple liquid was then filtered and rapidly acidified at 0° by addition to hydrochloric acid (250 c.c., *d* 1·16) (yield, 85—54%). Distillation in steam or superheated steam gave only 0·6—0·65 g. of 4-halogeno-2-naphthol per l., but yields exceeding 60% (on the amine taken) were obtained by distillation under ordinary pressure; vacuum distillation entailed considerable loss due to sublimation of the 4-halogeno-2-naphthol. When the excess of stannous chloride used above was diminished, a larger amount of coupled product was obtained (*i.e.*, coloured material sparingly soluble in hot aqueous sodium hydroxide).

Reduction of the above diazo-oxides in glacial acetic acid solution by stannous chloride–hydrochloric acid afforded no halogenonaphthol.

4-Iodo-2-naphthol.—4-Iodonaphthalene-1 : 2-diazo-oxide (15 g.) (Hodgson and Birtwell, *loc. cit.*) was boiled with alcohol (250 c.c.) and aluminium powder (3·75 g.); the reaction was complete in 4 hours. The product, worked up as in the case of the chloro-analogue, gave 8·0 g. (60%) of *4-iodo-2-naphthol*, which, crystallised from benzene and then from aqueous ethyl alcohol (charcoal), formed colourless needles, m. p. 128·5° (Found: I, 46·8. $C_{10}H_7OI$ requires I, 47·0%).

4-Iodo-1-benzeneazo-2-naphthol crystallised from glacial acetic acid in red felted needles, m. p. 176° (Found: I, 33·8. $C_{16}H_{11}ON_2I$ requires I, 33·9%), *4-iodo-2-naphthyl methyl ether* from light petroleum (charcoal) in plates, m. p. 67° (Found: I, 44·6. $C_{11}H_9OI$ requires I, 44·7%), and *4-iodo-2-naphthyl acetate* from light petroleum in colourless plates, m. p. 59° (Found: I, 40·6. $C_{12}H_9O_2I$ requires I, 40·7%).

4-Nitronaphthalene-1 : 2-diazo-oxide (2·15 g.) was refluxed with ethyl alcohol (40 c.c.), iron filings (5 g.), and copper sulphate crystals (2·5 g.) while water (40 c.c.) was added during 30 minutes. The alcohol was then distilled off, and the 4-nitro-2-naphthol extracted from the residue by the above procedure. Yield, 1·0 g. (52%).

The authors thank I.C.I. (Dyestuffs) Limited, for various gifts, and G. Turner, B.Sc., for some of the analyses.

Technical College, Huddersfield. [*Received, May 17th*, 1943.]

127.—*Evidence for the Sulphite and Sulphonate Structures of Hantzsch's Potassium Benzene*-syn- *and* -anti-*diazosulphonates.*

By Herbert H. Hodgson and Ewart Marsden.

Hantzsch's potassium benzene-*syn*- and -*anti*-diazosulphonates couple with diazotised *p*-nitroaniline, giving products for which his stereochemical formulæ do not account. The *syn*-compound behaves like a sulphite, $R{\cdot}N{:}N{\cdot}O{\cdot}SO_2K$, but the *anti*-compound is best represented as a sulphonate, $R{\cdot}N{:}N{\cdot}SO_3K$. Hantzsch's potassium benzene-*syn*-diazosulphonate is a mixture of his so-called *syn*- and *anti*-isomerides, wherein the *syn*- is rapidly converted into the *anti*-form, behaviour which accounts for the identity of his spectroscopic and conductometric data. The *syn*-(sulphite) forms of potassium and sodium *p*-nitrobenzenediazosulphonates have been prepared.

In his discussion of Hantzsch's theory of the constitution of the diazo-compounds Saunders states ("The Aromatic Diazo-Compounds and their Technical Applications," London, 1936, p. 188) that, if the theory is correct, it follows that every diazo-compound can exist in three isomeric forms, *viz.*, diazonium, *syn*- and *anti*-diazotates. Hantzsch was not able to cite any cases to prove his theory conclusively, but he sought chief support from three classes of compounds, *viz.*, the diazocyanides, the diazobenzenesulphonic acids, and the diazo-sulphonates. $Ar{\cdot}N{:}N{\cdot}SO_3K$. Evidence is now presented which proves that Hantzsch's stereochemical conception of *syn*- and *anti*-diazosulphonates is fundamentally wrong.

The diazosulphonates are known only in the two modifications of *syn*- and *anti*-forms, Saunders stating (*op. cit.*, p. 190) that no substance having the properties to be expected of a diazonium salt of sulphurous acid has been discovered to complete the family of isomers. In this respect, the stabilised compounds of diazonium salts with naphthalene- and other sulphonic acids must be either diazonium sulphites or diazo-sulphites, the colourless members probably having the former constitution. The following facts were the basis for Hantzsch's assertion that the two modifications above were stereoisomers: (1) The more deeply coloured *syn*-isomer had the power to couple with β-naphthol, and on standing in solution changed into the stable form, which did not couple and must therefore belong to the series usually termed *anti*. (2) Conductometric determinations showed the salts of both series to dissociate in solution into two ions, the *syn*-salt in addition giving evidence of hydrolytic dissociation. (3) A similarity of absorption spectra.

Bamberger (*Ber.*, 1894, **27**, 2586, 2930) suggested that the properties of the diazosulphonates, *viz.*, oxidation by iodine, coupling power, and decomposition by acids with liberation of sulphur dioxide, could just as well be explained by the sulphite formula $Ph{\cdot}N{:}N{\cdot}O{\cdot}SO_2K$, whereas the *anti*-diazosulphonates, which were non-reactive with iodine and did not couple, could be assigned the sulphonate formula, $Ph{\cdot}N{:}N{\cdot}SO_3K$, *i.e.*, with the azo-nitrogen attached to the sulphur atom. Claus (*J. pr. Chem.*, 1894, **50**, 239) reached the same conclusion, assuming normal potassium sulphite to be $KO{\cdot}SO_2K$. Saunders (*op. cit.*, p. 195) observes that the only unchallenged item is the spectroscopic evidence, which is in favour of Hantzsch. The alternative suggested by Blomstrand and Bamberger, that the normal *syn*-diazosulphonates were diazonium compounds $Ar{\cdot}\overset{\oplus}{N}{:}N\}\overset{\ominus\ominus}{SO_3}\overset{\oplus}{K}$, was discounted by Hantzsch on the grounds that they should give three ions in aqueous solution (whereas only two were found) and that the solution should be colourless or nearly so, in conformity with the colours of benzenediazonium salts generally, whereas they are red. It has now been found that the *syn*-form cannot be obtained pure but is always mixed with the *anti*-isomeride, into which it passes rapidly; the spectroscopic evidence of identity of form therefore receives an obvious explanation.

The Coupling of Diazotised p-*Nitroaniline with Potassium Benzene*-anti-*diazosulphonate.*—On Hantzsch's assumption that the potassium salt has the N–S link, the product formed by coupling with diazotised *p*-nitroaniline must have formula I*a* or *b*:

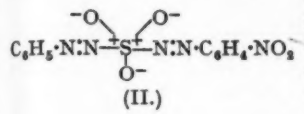
(I*a*.) $C_6H_5{\cdot}N{:}N{\cdot}SO_2{\cdot}O{\cdot}N{:}N{\cdot}C_6H_4{\cdot}NO_2$ $\qquad$ $C_6H_5{\cdot}N{:}N{\cdot}\overset{\ominus}{SO_3}\}\overset{\oplus}{N_2}{\cdot}C_6H_4{\cdot}NO_2$ (I*b*.)

This compound, which is readily formed and sufficiently stable when moist at 0° for subsequent reaction, couples readily with β-naphthol to give *p*-nitrobenzeneazo-β-naphthol, leaving benzene-*anti*-diazoniumsulphonate in solution, from which it may be recovered intact or, after oxidation, as a diazonium salt, which then couples with β-naphthol to give benzeneazo-β-naphthol. It follows, therefore, that the N–S link of the original *anti*-structure remains intact during the coupling reaction.

The Composite Character of Potassium Benzene-syn-*diazosulphonate.*—The *syn*-salt made according to the directions of Hantzsch (*loc. cit.*) is of variable composition and cannot be obtained free from the *anti*-isomeride. Washing with water, or even keeping in a moist state on the filter, rapidly brings about conversion of the *syn*- into the *anti*-form, as shown by change of colour from orange-red to yellow and deterioration in coupling power with alkaline β-naphthol (Bamberger, *Ber.*, 1894, **27**, 2930, records that analyses of the *syn*-compounds are rendered untrustworthy by rapid decomposition and molecular change). Moreover, Hantzsch's observation that the *syn*-compound reacts with copper sulphate with evolution of nitrogen is in accord with the sulphite formula, since conversion into benzenediazonium sulphate will be brought about and followed by decomposition by the cuprous salt thereby produced; on the other hand, copper sulphate only produces a green coloration with the *anti*-isomeride.

The Coupling of Diazotised p-*Nitroaniline with Potassium Benzene*-syn-*diazosulphonate.*—When the mixture which has been termed the *syn*-compound is coupled with diazotised *p*-nitroaniline, a precipitate (A) is formed

which couples with alkaline β-naphthol to form a mixture (B) of benzeneazo-β-naphthol and *p*-nitrobenzeneazo-β-naphthol, since on reduction (B) yields both aniline and *p*-phenylenediamine (identified by conversion into *p*-benzoquinone). The so-called *syn*-compound is therefore a mixture. Again, oxidation of the filtrate from (B) affords a mixture (C) of benzeneazo-β-naphthol and *p*-nitrobenzeneazo-β-naphthol, derived from the so-called *anti*- and *syn*-isomerides respectively in the original mixture. These experiments also show that in the so-called *syn*-compound the diazotised *p*-nitroaniline combines at the sulphur atom to form an N–S link and does not form a diazonium salt, otherwise the whole of the *p*-nitrobenzeneazo-component in mixture (A) would have been combined with β-naphthol in mixture (B), and (C) would have consisted of benzeneazo-β-naphthol only. If the *syn*-salt had the Hantzsch formula, the product with diazotised *p*-nitroaniline would be formulated as in (II), which is not possible on modern electronic theory. The formula of the product of the *syn*-compound with diazotised *p*-nitroaniline is therefore best represented by (III*a*); (III*b*), however, is not excluded. In either event the Hantzsch *syn*-structure with its N–S link is impossible, and the sulphite structure, which explains the experimental facts, must be preferred.



(II.)

(III*a*.) $C_6H_5\cdot N{:}N\cdot O\text{—}\overset{+}{S}\overset{+}{\text{—}}N{:}N\cdot C_6H_4\cdot NO_2$ (O⁻ and O⁻)

$C_6H_5\cdot\overset{+}{N}_2\}\overset{-}{O}\text{—}\overset{+}{S}\text{—}N{:}N\cdot C_6H_4\cdot NO_2$ (III*b*.) (O⁻ and O⁻)

Formation of the Potassium (*or Sodium*) p-*Nitrobenzene*-syn-*diazosulphonate*.—Hantzsch and Borghaus (*Ber.*, 1897, **30**, 89) state that the stable *anti*-form only is given by the nitrodiazobenzenes, but it has now been found that, when neutral *p*-nitrobenzenediazonium chloride is treated with potassium or sodium sulphite, a labile compound is formed which couples with alkaline β-naphthol, is oxidised by iodine, liberates sulphur dioxide with mineral acids, and couples with diazotised *p*-nitroaniline to form a complex which in turn couples with alkaline β-naphthol to form *p*-nitrobenzeneazo-β-naphthol in amount equivalent to half the total *p*-nitroaniline involved. The filtrate therefrom, when oxidised, affords *p*-nitrobenzeneazo-β-naphthol in amount corresponding to the other half of the *p*-nitroaniline. The labile compound, therefore, is analogous to the so-called *syn*-diazosulphonate from aniline.

Finally, potassium *p*-nitrobenzene-*anti*-diazosulphonate couples with diazotised aniline to form a complex, which reacts with alkaline β-naphthol to form only benzeneazo-β-naphthol, and the filtrate therefrom is oxidised to give *p*-nitrobenzeneazo-β-naphthol only, the exclusive results indicating that the initial *anti*-structure has been preserved in the complex.

Conclusions.—(1) Hantzsch's *syn*-formula for potassium benzene-*syn*-diazosulphonate cannot be correct, since the sulphur atom cannot be covalently attached to both diazo-groups in the various complexes described. (2) A sulphite formula correctly accounts for all the reactions, and this may be either $C_6H_5\cdot N{:}N\cdot O\cdot SO_2K$ or $C_6H_5\cdot\overset{+}{N}_2\}\overset{-}{O}\cdot SO_2K$ or an equilibrium mixture of both. (3) The *anti*-formula of Hantzsch is valid, and is in accord with the general behaviour of sulphonates. (4) The ready transformation in aqueous solution of the *syn*- into the *anti*-form is accounted for on the sulphite–sulphonate formulation by facile fission of the N–O link (as shown by coupling), which is favoured by the greater stability of quadricovalent sulphur (cf. the stable ·N:N·S· group in the diazo-sulphides with the far less stable ·N:N·O· group in those diazo-oxides whose constitution is beyond doubt) (cf. also recent work by Kenyon *et al.* on analogous isomerisations of sulphinic esters to sulphones). (5) The original view of Bamberger and Claus is more reasonable than that of Hantzsch in the light of modern chemical theory; *e.g.*, it is improbable that stereoisomeric structures in the *syn*-form contain an N–S link so unstable that fission occurs in the presence of alkaline phenols or naphthols, or even with the latter in the presence of sodium acetate, whereas in the *anti*-configuration this N–S link resists such rupture. (6) The colour of the sulphite (*syn*-compound) is in favour of a covalent N–O link. (7) The complexes prepared from both the *syn*- and the *anti*-isomerides by coupling with diazotised amine probably contain both structures. They are all very unstable with the exception of the one from potassium benzene-*anti*-diazosulphonate and diazotised *p*-nitroaniline, which may be dried at room temperature.

Experimental.

The Coupling of Diazotised p-*Nitroaniline with Potassium Benzene*-anti-*diazosulphonate*.—The *anti*-compound, prepared from aniline (9·3 g.) according to the directions of Hantzsch (*loc. cit.*), was salted out with brine and air-dried; it did not couple with alkaline β-naphthol. It was dissolved in water (200 c.c.), the solution filtered, and ice (50 g.) added, followed by a solution of *p*-nitrobenzenediazonium chloride (from 13·8 g. of *p*-nitroaniline) which had been neutralised with calcium carbonate. The yellow crystalline precipitate formed was collected, washed with ice-water (1500 c.c.) until free from diazonium salt, and stirred into β-naphthol (20 g.) dissolved in a slight excess of sodium hydroxide solution; the *p*-nitrobenzeneazo-β-naphthol formed had m. p. 237°, and 250° after recrystallisation from acetic acid. The remaining solution on air oxidation (slowly, or more rapidly by bubbling), or on addition of potassium chromate, or on neutralisation with dilute nitric acid, addition of alcohol to dissolve precipitated β-naphthol and then of lead nitrate, gave benzeneazo-β-naphthol, m. p. 125°, and m. p. 131° after recrystallisation.

Reactions of Potassium Benzene-syn-*diazosulphonate*.—(a) *With β-naphthol*. The unfiltered mixture of *syn*- and *anti*-compounds prepared according to the directions of Hantzsch (*loc. cit.*) from aniline (4·65 g.) was immediately treated with excess of alkaline β-naphthol, benzeneazo-β-naphthol (9·6 g.) being precipitated in amount corresponding to a ratio of 77·5% of *syn*- and 22·5% of *anti*-compound. A delay of only 15 minutes between preparation and coupling caused a decrease in the amount of *syn*-compound to 33%.

(b) *The composite character of Hantzsch's* syn-*compound*. The orange-red *syn*-potassium salt, removed as rapidly as possible after formation, was thoroughly pressed (but not washed, since this only served to convert the *syn*- into the

anti-form), and then coupled with alkaline β-naphthol. The precipitate of benzeneazo-β-naphthol was removed, and the filtrate oxidised as above; a further precipitate of benzeneazo-β-naphthol was then obtained derived from the *anti*-isomeride present in the initial orange-red crystals. However rapid the manipulation, there was always a substantial amount of *anti*-compound present (78% being a typical amount).

(c) *Coupling of a mixture of sodium benzene*-syn- *and* -anti-*diazosulphonates with diazotised* p-*nitroaniline.* Aniline (9·3 g.) was diazotised at 0° in dilute hydrochloric acid and the solution was neutralised with calcium carbonate, filtered, and added to crystallised sodium sulphite (25·2 g.) in water (50 c.c.); the mixture was kept at 0° for 15 minutes and then added to neutralised *p*-nitrobenzenediazonium chloride (from 13·8 g. of *p*-nitroaniline) in water (250 c.c.). The precipitated orange-yellow crystalline (plates) complex was rapidly washed with ice-water (1500 c.c.) until free from diazonium salt and then coupled with alkaline β-naphthol. The precipitate of benzeneazo- and *p*-nitrobenzeneazo-β-naphthol, m. p. 216°, was removed, and the filtrate oxidised as above, a mixture of the same azo-β-naphthols being obtained, m. p. 170°. Both mixtures, when reduced with zinc dust in boiling aqueous-alcoholic suspension, gave aniline (removed by steam-distillation) and *p*-phenylenediamine (by oxidation of the residual liquor with ferric chloride).

The Coupling of Diazotised Aniline with Sodium p-*Nitrobenzene*-anti-*diazosulphonate.*—A mixture at 0° of *p*-nitrobenzenediazonium chloride (from *p*-nitroaniline, 13·8 g.) in the minimum of water (150 c.c.) with a saturated solution of sodium sulphite (25·2 g.) and anhydrous sodium carbonate (6 g.) was kept for 90 minutes; it then no longer coupled with alkaline β-naphthol. Sodium chloride was added, and the yellow precipitate of sodium *p*-nitrobenzene-*anti*-diazosulphonate collected, washed with brine, dried (*ca.* 50% yield), and redissolved in water (150 c.c.), and the solution filtered and treated with neutral benzenediazonium chloride (from 4·65 g. of aniline). The yellowish-brown amorphous precipitate obtained, which was moderately stable when moist at 0°, was washed free from diazotised aniline and coupled with alkaline β-naphthol. The precipitated benzeneazo-β-naphthol (m. p. 126°, and 131° after recrystallisation from acetic acid) was removed; the filtrate, when oxidised as above, gave a precipitate of *p*-nitrobenzeneazo-β-naphthol, m. p. 246°, and 250° after recrystallisation from acetic acid.

Sodium p-*Nitrobenzene*-syn-*diazosulphonate coupled with Diazotised Aniline.*—A solution of crystallised sodium sulphite (25·2 g.) was added to one of neutral *p*-nitrobenzenediazonium chloride (from 13·8 g. of *p*-nitroaniline) (total vol., 300 c.c.), and the mixture kept at 0° for 90 minutes, then treated with neutral benzenediazonium chloride (from 9·3 g. of aniline) (vol., 200 c.c.) at 0°. The orange crystalline (plates) precipitate was washed at 0° with ice-water (2 l.) until the filtrate no longer coupled with alkaline β-naphthol, and then stirred with excess of alkaline β-naphthol. The mixture of benzeneazo- and *p*-nitrobenzeneazo-β-naphthols formed (m. p. 162—165°) was removed; the filtrate on oxidation gave a similar precipitate (m. p. 170°). Both precipitates afforded aniline and *p*-phenylenediamine on reduction.

Sodium p-*Nitrobenzene*-syn-*diazosulphonate coupled with Diazotised* p-*Nitroaniline.*—This complex, prepared as described above, was obtained as a thick orange-yellow precipitate, which was washed free from the excess of diazotised *p*-nitroaniline. A portion of it was treated with excess of alkaline β-naphthol; the precipitated *p*-nitrobenzeneazo-β-naphthol (5·2 g.) had m. p. 246°. From the filtrate, after oxidation, a further precipitate of the same compound was obtained (5·0 g.), m. p. 246°. Both precipitates, crystallised from glacial acetic acid, gave pure *p*-nitrobenzeneazo-β-naphthol, m. p. 250°.

The authors thank I.C.I. (Dyestuffs) Ltd. for gifts of chemicals.

Technical College, Huddersfield. [*Received, June 2nd,* 1943.]

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128. *Rubber, Polyisoprenes and Allied Compounds. Part V. The Chemical Linking of Rubber and of Other Olefins with Phenol–Formaldehyde Resins.*

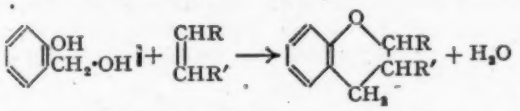
By J. I. Cunneen, E. Harold Farmer, and H. P. Koch.

Rubber, isoprenic olefins, and doubtless most olefinic substances combine in virtue of their unsaturation with the condensation products of phenol and formaldehyde to give chroman derivatives. The detailed structure of the combination products, the relation of chroman-formation to the formation of phenol–formaldehyde resins, and the significance of certain ancillary features of the reaction are discussed.

Rubber combines readily with maleic anhydride (Bacon and Farmer, *Proc. Rubber Tech. Conf.*, 1938, p. 256) up to a limit of one molecule of the latter per isoprene unit of the former. The comparative ease of occurrence of this reaction made it seem feasible to use maleic and similar unsaturated anhydrides (or acids) as a means of linking rubber chemically with various types of hydroxylic compound, the ethylenic carbon pairs of the maleic molecules serving to form C–C links with the rubber, and the anhydro-groupings to form ester links with hydroxy-compounds. Although it was possible to carry out this linking process successfully in a number of examples, the combination of rubber with phenol–formaldehyde resins could be much more satisfactorily effected if the rubber–maleic anhydride compound was not pre-formed, but, instead, a somewhat oxidised rubber together with maleic anhydride, phenol, and formaldehyde were simply heated together until resin formation occurred (Redfarn and Schidrowitz, B.P. 507,995). Subsequently, it was found that considerably oxidised rubber (oxygen, *ca.* 10—13%; *M*, 3000—4000) reacted more readily than slightly oxidised rubber, the product being a thermo-setting resin of Bakelite type, remarkable in possessing valuable residual thermoplastic properties. Investigation of the chemical reaction by which this resin is produced has given rather unexpected results in the field of additive reactions, and has thrown new light on the process of resinification.

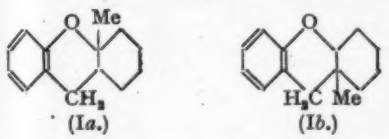
It was soon discovered that maleic anhydride could be satisfactorily replaced by oxalic or acetic acid, and no evidence could be gained that any appreciable degree of esterification of the anhydride units by the hydroxylic phenol–formaldehyde components occurred. Hence the maleic anhydride clearly functioned largely as a mild acid catalyst. The great improvement in the ease of condensation which followed the replacement of lightly oxidised by considerably oxidised rubber seemed at first to indicate that a reaction of aldol type took place between the ·CHO or ·COMe end-groups of the shortened rubber chains and the keto-tautomer

of phenol, or alternatively that elimination of water occurred between hydroxyl groups in the oxidised rubber and the aromatic nuclei of the phenol. Thorough experimental examination, however, of these possibilities led to their dismissal from further consideration (the experimental details have been omitted). There remained, then, no very reasonable alternative to the conclusion that rubber, and therefore probably most olefinic substances, are able, in virtue of their olefinic unsaturation, to combine with phenol and formaldehyde at some stage in the intercondensation of the latter, and this conclusion was reinforced by certain experiments carried out by Hilditch and Smith in 1935 (*J. Soc. Chem. Ind.*, **54**, 111) which strongly indicated that drying-oil esters are able because of their unsaturation to combine with a simple *p*-cresol–formaldehyde condensation product. Any remaining doubt as to the capacity of olefinic materials to unite or condense with simple phenol–formaldehyde condensation products was removed by the publication at this point of a paper by Hultzsch (*J. pr. Chem.*, 1941, **158**, 275; *Chem. Abs.*, 1942, **36**, 849), in which the result of heating saligenin with styrene was

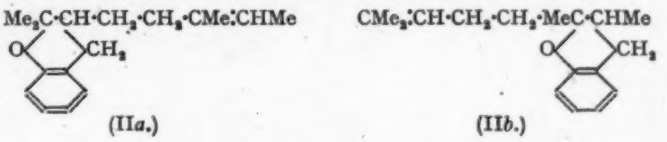


reported to be the formation of 2-phenylchroman, and that of heating several other simple phenol–formaldehyde condensation products containing ·OH and ·CH_2·OH groups in *o*-positions with olefinic alcohols, esters, etc., was the formation of analogous chroman derivatives. Curiously enough, however, *cyclo*hexene was reported not to undergo condensation with saligenin.

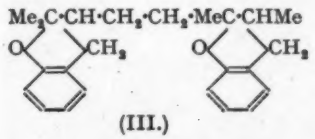
We found on examining the behaviour towards saligenin of the two simple analogues of rubber, 1-methyl*cyclo*hexene and dihydromyrcene, that reaction in each case occurs readily at 180°, giving by loss of water a non-hydroxylic, oxygen-containing condensation product having the general properties and empirical composition to be expected for chroman structures of the type reported by Hultzsch. The di-olefin, dihydromyrcene, however, formed a di- as well as a mono-saligenino-condensation product, the two compounds resembling one another in containing no active hydrogen, but differing in containing respectively no hydrogenisable double bond, and one such bond. For the *compound* from 1-methyl*cyclo*hexene, (I*a*) and (I*b*) are possible



(I*a*.) (I*b*.)



(II*a*.) (II*b*.)



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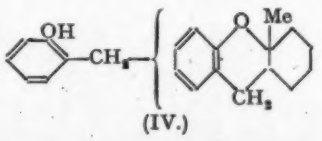

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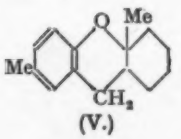


(V.)

formulæ, but since any addition of a reagent to an unsymmetrical olefin CRR′:CH_2 or CRR′:CHR″ normally proceeds almost entirely in one direction (as determined by the relative polarity of the ethylenic carbon atoms) (I*b*) is unlikely to represent any considerable proportion of the product unless the addition reaction involves radical forms (see below). Similarly for the two compounds from dihydromyrcene the monosaligenin *compound* is likely to be mainly (II*a*) or (II*b*), and the disaligenin *compound* (III). It was very significant from the point of view of successful resin-formation, however, that the monosaligenin compound from 1-methyl*cyclo*hexene was accompanied by a small amount of a disaligenin *compound*, $C_{21}H_{24}O_3$. This contained one atom of active hydrogen per molecule and apparently represented the simplest possible example of the linking of a polycondensed phenol–formaldehyde chain (*i.e.*, a Novolak) to the olefin.* This compound is formulated in (IV), the point of attachment of the hydroxybenzyl group to the aromatic nucleus of the chroman unit being presumably *o*- or *p*- to the chroman oxygen.

When purified rubber (1 mol.) in benzene was heated with saligenin in two different proportions (0·18 and 0·27 mol.) two distinct oxygenated products were formed. These proved to contain hydroxylic (presumably phenolic) as well as ethereal oxygen, in the ratios 1 : 2 and 5 : 8, so indicating that most of the oxygen was present in simple chroman units such as those in (III), and that roughly one chroman unit per 14 or per 8 isoprene units of the rubber was present. Not more than 1 in 2 or 5 in 8 (respectively) of the chroman units could thus be carrying a hydroxybenzyl substituent, or, if still larger phenol–formaldehyde substituents than hydroxybenzyl were present, then the proportion of chroman units carrying side chains (of any kind) would be smaller still. Confirmation of the constitutions advanced above has been sought by spectrographic means.

Absorption Spectra.—Webb and others (*J. Org. Chem.*, 1939, **4**, 389) gave data for the light-absorption in hexane solution of a number of alkyl-substituted phenols, chromans, and coumarans, all of which exhibit a group of two or more narrow bands in the region 2700—2900 A. They found that the formation of chroman or coumaran rings by cyclisation of *o*-alkylphenols is regularly associated with a well-marked increase and

* No long Novolak chains were to be expected, since an excess of olefin was always used.

bathochromic shift of absorption, and that the exact location and intensity interrelationships of the fine structure bands is also highly characteristic of any given compound. We have therefore determined the ultra-violet absorption spectra (in *cyclo*hexane solution) of saligenin and its various condensation products for purposes of identification.

Saligenin itself (Fig. 1, curve *a*) gives rise to two bands near 2730 and 2800 A., closely similar to the spectra of *o*-cresol (Hogness, Sidwell, and Zscheile, *J. Biol. Chem.*, 1937, **120**, 251) and *o*-allylphenol (Webb *et al.*, *loc. cit.*) which only differ in the nature of the *o*-alkyl substituent. This absorption is intensified and displaced towards longer wave-lengths on passing to the compound of saligenin with methyl*cyclo*hexene (I*a*) (cf. Fig. 1, curve *b*), which is characterised by two steep maxima situated at precisely the same wave-lengths as the two bands of 2 : 2-dimethylchroman measured by Webb *et al.* (2775 and 2845 A.; minimum at 2815 A.). The width and relative height of the bands are also the same for both compounds, although all our intensities are consistently higher than Webb's on the absolute molecular scale ($\varepsilon = 3100$ at 2845 A.). The new compound evidently contains the same chromophoric grouping as 2 : 2-dimethylchroman, and its formulation as a methyl-substituted hexahydroxanthen (I*a*) may be considered as established beyond any doubt.

FIG. 1.

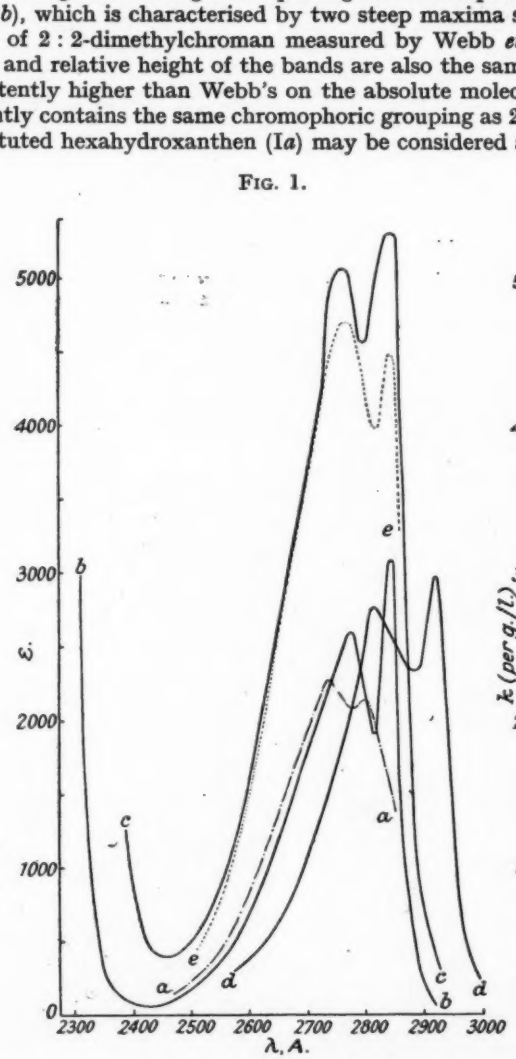
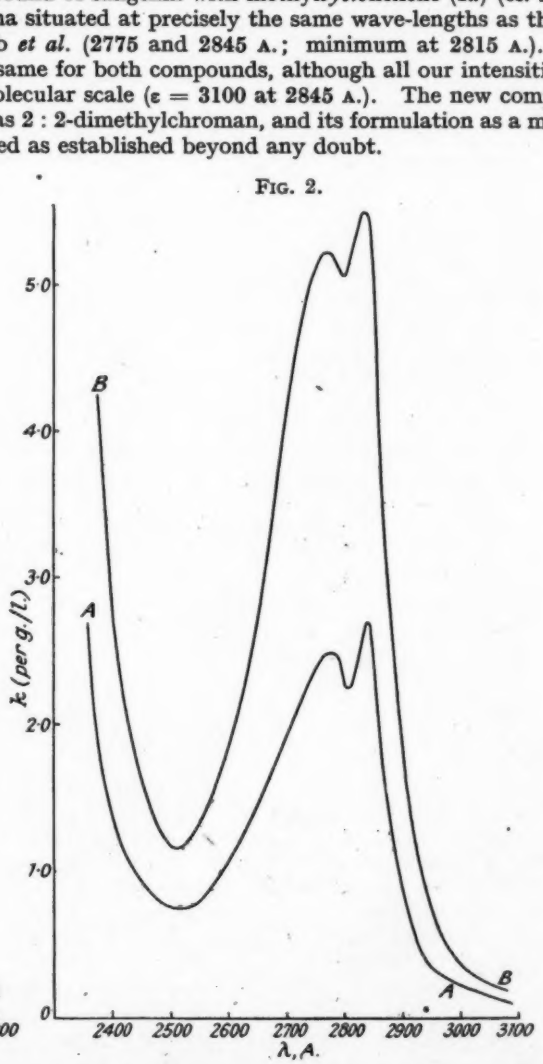


FIG. 2.



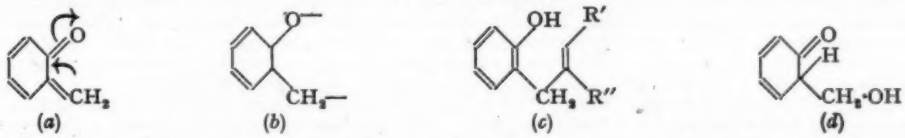
Again, the two substances $C_{17}H_{24}O$ and $C_{24}H_{30}O$ obtained by condensation of saligenin with dihydromyrcene, at one and at both (respectively) of the double bonds of the latter, exhibit absorption curves identical with the above. The molecular extinction coefficients at 2845 A. are now 3000 and 5650 respectively, in good agreement with the proposed structures (II, *a* or *b*) and (III) which contain the 2 : 2-dialkylated chroman chromophore once or twice in the dihydromyrcene chain. Although the spectra of (II*a*) and (II*b*) would be indistinguishable, it seems likely that all our chroman derivatives must carry the extra methyl groups derived from the olefin in the 2-, and not the 3-position in order to produce complete identity with the spectrum of Webb's prototype.

Curve *c* of Fig. 1 shows the extinction values of the solid hydroxybenzyl-substituted chroman derivative (IV). Its total absorption must be expected to bear close resemblance to the sum of the separate absorptions contributed by the *o*-hydroxybenzyl and the (nuclear-substituted) chroman chromophores which are effectively isolated from one another in the compound molecule (cf. Jones, *Chem. Rev.*, 1943, **32**, 2). This sum is graphically represented by the dotted curve *e*, except in the important respect that no allowance is made for the effect of nuclear substitution on the spectrum of the chroman system shown in curve *b*. We have been able

to test that effect directly as regards the *p*-position by synthesising the *p*-methyl *derivative* (V) (curve *d*). The general appearance of the spectrum remains unchanged, but a significant displacement of the maxima to 2815 and 2920 A. is observed. Since it is known that such bathochromic shifts are largely independent of the precise nature of the alkyl substituent (methyl, ethyl, and benzyl groups all displace the absorption of benzene to longer wave-lengths; cf. Ley and Dirking, *Ber.*, **1934**, **67**, 1333), it must be concluded that the hydroxybenzyl derivative (IV), in giving rise to a spectrum that terminates very abruptly beyond 2845 A., cannot contain the substituent affixed in the *p*-position. On the other hand, the difference between the observed and the constructed curve, *c* and *e*, can be well accounted for by formulating the hydroxybenzylchroman with the hydroxybenzyl group attached at the *o*-carbon atom. Both phenol and *o*-cresol (but not *p*-cresol) exhibit maximum absorption at the same wave-lengths (Wolf and Herold, *Z. physikal. Chem.*, 1931, *B*, **13**, 229), and the near-ultra-violet band of 2-methylcoumaran is considerably intensified but not displaced as the result of *omm'*-trisubstitution (Webb *et al.*, *loc. cit.*). It has, indeed, been stated as a general rule for aromatic compounds that *o*-substitution produces only slight, and *p*-substitution relatively marked, bathochromic effects (Morton and Stubbs, J., 1940, 1347).

Finally, the absorption spectra of the two rubber–saligenin compounds (containing 2·25% and 4·15% of total oxygen respectively) were measured in solutions of *cyclo*hexane containing 10% of ethyl alcohol. This choice of solvent was governed by the difficulty of obtaining optically clear solutions, but it was found that none of the curves of Fig. 1 was appreciably altered by addition of the alcohol. Purified rubber itself does not exhibit selective absorption in the quartz ultra-violet, and the typical steep maxima at 2845 and near 2775 A. of the curves *A* and *B* (Fig. 2) obtained for the two rubber derivatives must clearly be attributed to the presence of the chroman chromophore attached to the rubber chain. Allowance being made for increased general absorption, and a 5 : 8 ratio of phenolic to ethereal oxygen (see above) being assumed, the maximum specific extinction coefficient of curve *B* indicates that an average number of one in every ten isoprene units has reacted with a saligenin or *o*-substituted saligenin group. This figure is rather lower than the value of one in eight obtained from the total oxygen content, but certainly serves to show that the bulk of the saligenin must be attached to the rubber molecule by way of the chroman linkage.

Mechanism and Course of Reaction.—The precise mechanism by which the reactive groups of saligenin or other *o*-hydroxybenzyl alcohols unite with olefinic centres is not easy to determine. It might be supposed that the phenolic alcohol loses water internally to give momentarily either a strongly polarised form (*a*) or a resonating radical form (*b*), or else condenses directly with the olefin to give (*c*) as intermediate. The last course is not a likely one for non-benzenoid primary alcohols to pursue, and the lability of the hydroxyl group must arise from the nearness of the phenolic nucleus. This being so, probably the keto-form (*d*) of the phenolic



(*a*) (*b*) (*c*) (*d*)

alcohol is responsible for the reaction, undergoing internal dehydration to give the vinyl ketone (*a*). If combination of this ketone with the olefin occurred in Diels–Alder fashion (cf. the dimerisation of methyl vinyl ketone, Alder *et al.*, *Ber.*, 1941, **74**, 905, 926) to some extent through the form (*b*) and not wholly ionically through (*a*), the final condensation products would be likely to contain many isomeric forms (*e.g.*, I*b* as well as I*a*). The spectrographic evidence, however, does not point to the existence of the additional forms which would arise by *two*-direction addition of olefin to ketone.

As regards the conclusion that attachment of the hydroxybenzyl side chain in (IV) is restricted to the *o*-position in the chroman system (and this appears to apply also to the points of junction of the side chains in the rubber derivatives), it should be pointed out that the restriction may well not hold between phenol–formaldehyde units *throughout* the longer Novolak chains which would normally be formed where higher proportions of phenol and formaldehyde to olefin and an acid condensing catalyst were used. Also, it is quite likely that when maleic anhydride is used as the acid catalyst some or all of it ultimately combines with the phenol–formaldehyde condensation products, since Hultzsch found that ethyl maleate combines readily with these. The superior ease of combination of highly oxidised rubber over rubber hydrocarbon appears to be solely a function of miscibility of the reactants. The greatly shortened, oxygenated chains of the highly oxidised rubber (*M*, 3000—4000) dissolve fairly readily in boiling phenol, whereas rubber is insoluble.

The rubber-linked Novolaks formed in presence of an acid catalyst are capable of being cross-linked to yield three-dimensional molecular networks of the Bakelite type when heated in the ordinary way with hexamethylenetetramine. The resulting thermosetting products, however, soften when they are heated to 120—130° and harden again when they are cooled.

Experimental.

1-*Methyl*cyclo*hexene*.—The hydrocarbon, b. p. 110°, was obtained by dehydration of 1-methyl*cyclo*hexanol in the presence of a little iodine (Found : C, 87·45; H, 12·65; I.V., 265. Calc. for C_7H_{12} : C, 87·5; H, 12·5%; I.V., 265).

o-*Hydroxybenzyl Alcohol*.—Commercial saligenin, crystallised twice from ethyl alcohol–benzene (15 : 85 by vol.) formed colourless plates, m. p. 86° (Found : C, 67·85; H, 6·5. Calc. for $C_7H_8O_2$: C, 67·7; H 6·44%).

12-*Methyl*-1 : 2 : 3 : 4 : 12 : 13-*hexahydroxanthen* (I*a*).—Saligenin (40 g.) was heated with excess of 1-methyl*cyclo*-

hexene (200 c.c.) for 4 hours at 180° in sealed tubes. The tubes, on cooling, contained a pale yellow solution and a little water; the latter was removed with anhydrous copper sulphate. After the excess of olefin had been removed by distillation at reduced pressure a syrup (54 g.) remained. This syrup was dissolved in benzene (500 c.c.), washed twenty times with aqueous 2N-caustic potash (4 l.), and finally with water until neutral. The benzene solution was dried, and the solvent removed by distillation, leaving a pale yellow, mobile oil (43 g.). Fractional distillation of this oil, through a Fenske column, furnished 12-*methyl*-1 : 2 : 3 : 4 : 12 : 13-*hexahydroxanthen* (30 g.), a colourless, non-solidifying, mobile oil, b. p. 138—139°/10 mm. (Found : C, 83·15; H, 9·0. $C_{14}H_{18}O$ requires C, 83·17; H, 8·9%). A brown thermoplastic residue (13·0 g.) remained.

The oily condensation product did not possess ketonic or aldehydic properties and was not hydrolysable. A sample of it did not absorb hydrogen when shaken for 6 hours with the gas in presence of Adams's catalyst; a similar sample failed to liberate methane when treated with methylmagnesium iodide according to Bolland's modification of the Zerewitinov method. The condensation product, therefore, was an ether, without non-benzenoid unsaturation or hydroxyl groups.

5-*o*-*Hydroxybenzyl*-12-*methyl*-1 : 2 : 3 : 4 : 12 : 13-*hexahydroxanthen* (IV).—The undistillable thermoplastic residue (2 g.) was purified by dissolving it in benzene–petroleum (1 : 1 by vol.; 300 c.c.), running the solution through a column of alumina, and well washing the adsorbate with the same solvent (2 l.). The filtrate gave on evaporation the *compound* (IV) (1·2 g.), in which the *o*-hydroxybenzyl group, as shown by spectrographic examination, occupied the 5-position. This was an amorphous resinous solid (Found : C, 81·8; H, 8·0; OH, 5·3. $C_{21}H_{24}O_2$ require C, 81·8; H, 7·8; OH, 5·5%).

Dihydromyrcene.—Myrcene, prepared from bay oil (*Pimenta acris*) by the method of Power and Kleber (*Pharm. Rundschau*, 1895, **13**, 60), was reduced with sodium and alcohol as described by Semmler and Mayer (*Ber.*, 1911, **44**, 2010). The hydrocarbon, after being twice distilled over sodium through a Fenske column, boiled at 58—59°/16 mm. (Found : C, 87·05; H, 13·0; I.V., 364. Calc. for $C_{10}H_{18}$: C, 86·9; H, 13·1%; I.V., 368).

Monosaligenino-dihydromyrcene.—Saligenin (24 g.) was heated with dihydromyrcene (120 c.c.) for 2 hours at 180° in a sealed tube. The condensate was isolated in the usual manner and the yellow oil (32·6 g.) so obtained was fractionally distilled. *Monosaligenino-dihydromyrcene* (20·2 g.), b. p. 118°/0·05 mm., probably consisting mainly of 2 : 2-*dimethyl*-3-(γ-*methyl*-Δ$^{\gamma}$-*pentenyl*)*chroman* (II*a*), was first obtained (Found : C, 83·4; H, 9·9. $C_{17}H_{24}O$ requires C, 83·5; H, 9·85%). Further distillation gave nearly pure *disaligenino-dihydromyrcene* (5·4 g.), a viscous brown syrup, b. p. 200—205°/0·05 mm. Purification of the latter by adsorbing it on alumina from solution in petroleum, followed by elution of the adsorbate with benzene–petroleum (1 : 1 by vol.), gave an almost colourless syrup, doubtless α-(2 : 2-*dimethylchromanyl*-3)-β-(2 : 3-*dimethylchromanyl*-2)-*ethane* (III) (Found : C, 82·3; H, 8·7. $C_{34}H_{50}O$ requires C, 82·3; H, 8·6%). The monosaligenino-compound (0·2659 g.), in ethanol solution, absorbed hydrogen (24·8 c.c. at N.T.P.) equivalent to one double bond per molecule when shaken for 6 hours with Adams's catalyst (0·1 g.). The disaligenino-compound under the same conditions did not absorb hydrogen. Neither derivative gave any methane with methylmagnesium iodide under Bolland's modified conditions of Zerewitinov hydroxyl determination, and neither showed ketonic or aldehydic properties or was hydrolysable.

Rubber.—For convenience, a "sol" fraction of rubber, obtained by partial dissolution of crepe rubber in light petroleum (b. p. 40—60°), was employed. The crepe rubber was cut up and thoroughly extracted with acetone in the usual manner, and the residue then extracted with light petroleum in the all-glass modification of Pummerer, Andriessen, and Gündel's apparatus described by Bloomfield and Farmer (*Trans. Inst. Rubber Ind.*, 1940, **16**, 69). In the latter operation the extracts obtained in the first 48 hours were rejected as containing oxygenated rubber, and the later extracts were well mixed and their rubber content precipitated by addition of excess of 95% alcohol. The solvent and alcohol adhering to the rubber were removed by evaporation at 10 mm. pressure, and the rubber finally dried for 48 hours at room temperature and 10^{-5} mm. pressure. The rubber so obtained was kept under a high vacuum in the dark (Found : C, 88·05; H, 11·95; I.V., 371; *M*, 361,000. Calc. for C_5H_8 : C, 88·2; H, 11·8%; I.V., 372).

Saligenino-rubber.—Rubber (1·0 g.) was dissolved in toluene (25 c.c.) and heated with saligenin (0·33 g.) in a sealed tube containing oxygen-free nitrogen for 4 hours at 180°. After cooling, the tube contained a pale yellow solution and some water. Benzene (150 c.c.) was added, and the solution dried over anhydrous sodium sulphate, filtered, and concentrated under nitrogen at reduced pressure to 35 c.c. The clear solution so obtained was poured into an excess of ethyl alcohol, which precipitated the saligenino-rubber as a white rubber-like solid, leaving the self-condensation products of saligenin in solution. The precipitate was washed once with ethyl alcohol and thoroughly dried for 48 hours at 10^{-5} mm. by distillation of all solvent into a liquid-air trap (Found : C, 86·5; H, 11·25; OH, 0·8%; *M*, 119,000). Assuming that all the non-hydroxylic oxygen is ethereal, we calculated that one chroman linkage was present per 14 isoprene units (cf. the value found spectroscopically). A second saligenino-rubber, a white rubber-like solid, was prepared by heating rubber (1·8 g.) in toluene with a larger proportion of saligenin (0·9 g.) than was used in the foregoing experiment (Found : C, 85·3; H, 10·55; OH, 1·8%; *M*, 69,000). In this derivative one chroman linkage was present per eight isoprene units as calculated from the above analytical data.

7 : 12-*Dimethyl*-1 : 2 : 3 : 4 : 12 : 13-*hexahydroxanthen* (V).—2-Hydroxy-5-methylbenzyl alcohol, m. p. 105° (3 g.), was heated with 1-methyl*cyclo*hexene (15 c.c.) for 3 hours at 180° in a sealed tube. The pale yellow liquid product was freed from water by drying over anhydrous sodium sulphate, and then from solvent. The syrupy residue (3·8 g.) was dissolved in "AnalaR" benzene, and the solution washed twenty times with 2N-aqueous potassium hydroxide. The solvent was then removed, and the residue (3·3 g.) fractionally distilled. The first fraction had b. p. 147—150°/10 mm. (Found : C, 82·95; H, 9·4. $C_{15}H_{20}O$ requires C, 83·25; H, 9·3%), and the non-homogeneous residue consisted of substances of somewhat higher oxygen content.

Spectrographic Measurements.—The spectra were recorded on Kodak B-10 plates, using a Spekker Photometer and Hilger Small Spectrograph, which gives a dispersion of 35 A./mm. in the region of 2800 A. *cyclo*Hexane and ethyl alcohol were both purified for spectroscopic use.

We thank Dr. W. T. Chambers and Miss H. Rhodes for carrying out the microanalyses in this work, which forms part of the programme of fundamental research on rubber undertaken by the Board of the British Rubber Producers' Research Association.

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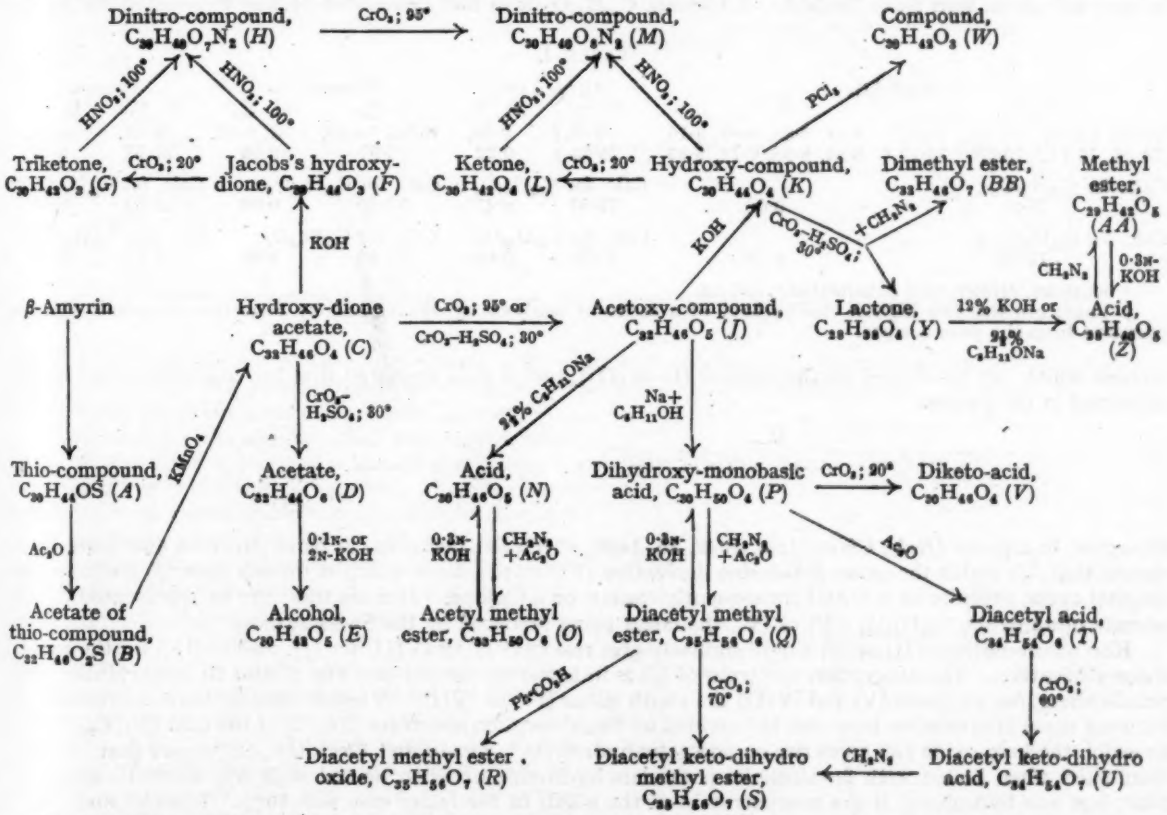
[*Received, August 9th*, 1943.]

129. *The Triterpene Group. Part X. A Continuation of Parts II and V.*

By J. C. E. Simpson and R. A. Morton.

The studies initiated in Parts II and V have been extended (see chart below and Table II for summary). The previous hypothesis of the presence of an aromatic ring in the β-amyrin derivative (*F*) and its congeners is withdrawn, and the results obtained by a study of these compounds are critically considered with reference to the recent publications of Ruzicka, Kon, and their co-workers. It is concluded that neither the Ruzicka (I) nor the Kon (III) formulation of (*F*) accounts for the properties of certain derivatives of this substance, and this is regarded as due to incorrect siting of the chromophore of (*F*). The substances discussed have been examined both chemically and spectrographically, and nitro-derivatives of the cholesterol series have been included in the survey for comparative purposes. Generalisations are made respecting the scope and limitation of the Liebermann–Burchard and the tetranitromethane reaction for the diagnosis of unsaturation in polycyclic hydroaromatic compounds.

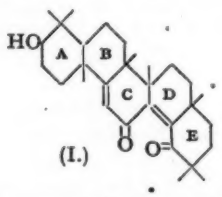
In Part II (J., 1938, 1313) one of us expressed the view that the compound $C_{30}H_{44}O_3$ (*F* in chart), obtained originally from β-amyrin by mild sulphur dehydrogenation and subsequent oxidation (Jacobs and Fleck, *J. Biol. Chem.*, 1930, **88**, 137), contains an aromatic ring. The evidence on which this conclusion was based consisted in the resistance to further oxidation of a supposed acetoxy-lactone (*J*) obtained from the acetate (*C*) of (*F*) by means of chromic anhydride, the absence of unsaturation reactions in both (*C*) and (*J*), and the position of the ultra-violet absorption maximum of (*C*). The intensity of this maximum (log ε = *ca.* 4) is clearly too high for an *isolated* aromatic ring, and it was considered that this factor might be due to the oxygen atoms in these substances being so located as to exert an auxochromic effect.* Continued study, however, showed that the dual properties of high-intensity absorption spectra and negative unsaturation tests persisted throughout an entire series of substances related to (*C*) and (*J*), and it became impossible to account for both sets of properties except by writing intrinsically improbable structures; in addition, efforts to isolate an aromatic



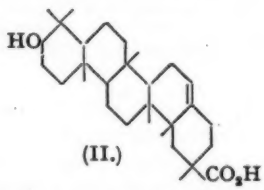
polybasic acid by nitric acid oxidation failed. At this point, the problem had to be temporarily laid aside. In the meantime, Ruzicka and Jeger (*Helv. Chim. Acta*, 1941, **24**, 1236) have shown that the compound (*F*)

* In Part II no attempt was made to give formal expression to this point owing to insufficient evidence. Commenting on this, Ruzicka, Müller, and Schellenberg (*Helv. Chim. Acta*, 1939, **22**, 767) have rightly pointed out the inadequacy of an isolated aromatic ring to account for the intensity of the absorption. On the other hand, Picard and Spring (J., 1941, 35, ll. 37, 38) state categorically that "an examination of its reactions led this author to the view that it [*i.e.*, (*F*)] contains an isolated benzenoid ring;" but such a view was not expressed in the paper to which they refer, and the phrase "isolated benzenoid ring" or its equivalent does not occur in it.

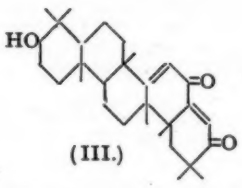
is not, as had been generally supposed, a keto-diol, but a hydroxy-dione, which condenses with hydrazine under drastic conditions to form a pyridazine derivative. It therefore contains two, and not three, double bonds, and the hypothesis of an aromatic ring is thus no longer tenable. On the basis of the spectrographic evidence and the pyridazine reaction, the Swiss authors have represented the hydroxy-dione (*F*) by the expression (I). Bilham, Kon, and Ross (J., 1942, 532, 535, 540) have adduced much evidence in favour of formula (II) for oleanolic acid, on the basis of which, as Kon and Ross (J., 1942, 741) have pointed out, the hydroxy-dione must be represented as (III). In view of these recent publications we record our own uncompleted experiments, which were carried out mainly in 1939 and 1940.



(I.)



(II.)



(III.)

The compound (*J*) was originally obtained in rather impure condition by Jacobs and Fleck (*loc. cit.*) as a concomitant of the hydroxy-dione by permanganate oxidation of the parent thio-compound (*A*, as benzoate). As Jacobs's hydroxy-dione was believed to be a keto-diol, the formation of (*J*) was explained (J., 1938, 1313) by the mechanism $>CH\cdot CO^- \longrightarrow >CO\ HO_2C^-$, with subsequent lactonisation on the (tertiary) hydroxyl group, and it was accordingly formulated as $C_{32}H_{44}O_5$, derived from $C_{32}H_{46}O_4$. However, all of many analyses which have been obtained for the acetoxy-compound (*J*), the hydroxy-compound (*K*), the related ketone (*L*) (carbonyl in position 2), and the oxime of the last, consistently favour a formula with two additional hydrogen atoms, as can be seen from Table I. A formula $C_{30}H_{44}O_4$ is in fact demanded by any expression for an O_4-

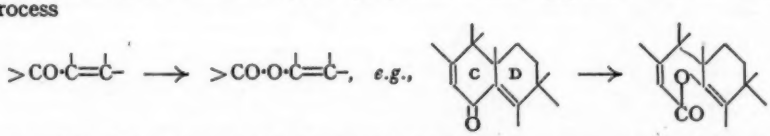
TABLE I.

Acetate (*J*).		Alcohol (*K*).		Ketone (*L*).		Oxime.	
C, %.	H, %.	C, %.	H, %.	C, %.	H, %.	C, %.	H, %.
75·06, 75·02, 75·11, 74·87, 75·06, 75·11,* 75·23,* 75·17 *	8·84, 8·85, 9·09, 9·16, 8·94, 8·98, 9·12, 8·86	76·61,† 76·25 †	9·39, 9·22	76·95, 76·90, 76·97	8·92, 8·92, 9·06	74·49, 74·77	9·12, 9·02
Calc. for $C_{32}H_{46}O_5$: 75·26	9·08	Calc. for $C_{30}H_{44}O_4$: 76·87	9·47	Calc. for $C_{30}H_{42}O_4$: 77·20	9·08	Calc. for $C_{30}H_{43}O_4N$: 74·80	9·00
Calc. for $C_{32}H_{44}O_5$: 75·55	8·72	Calc. for $C_{30}H_{42}O_4$: 77·20	9·08	Calc. for $C_{30}H_{40}O_4$: 77·53	8·68	Calc. for $C_{30}H_{41}O_4N$: 75·11	8·58

* Ruzicka, Müller, and Schellenberg, *loc. cit.*

† These are the two highest (for carbon) of a series of analyses by Weiler and by Schoeller of various samples prepared from the pure acetate.

lactone which can be written on the basis of (I) or (III), and it thus appeared that the oxidation of (*C*) to (*J*) consisted in the process

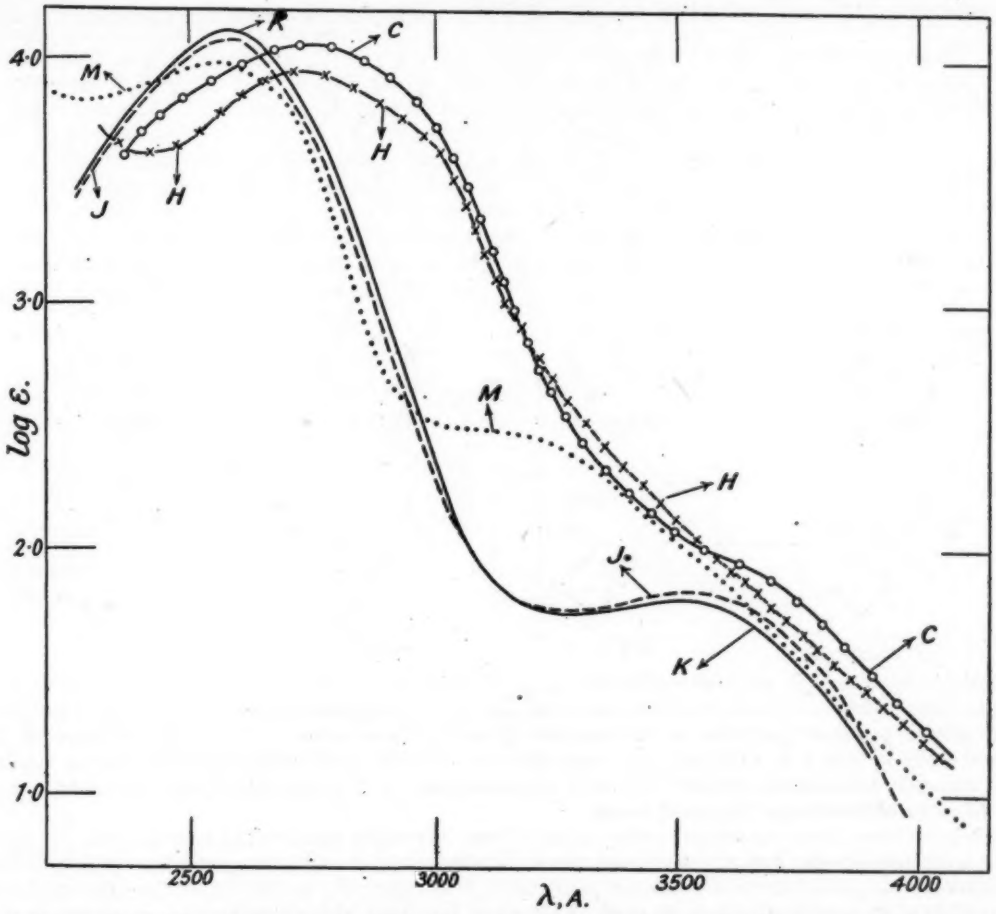


However, in a paper (*Helv. Chim. Acta*, 1942, **25**, 1409) which has just come to hand, Ruzicka and Jeger have shown that (*J*) yields the same pyridazine derivative (VI) as (*C*), from which it follows that (*J*) contains the original cyclic skeleton of (*C*), and consequently cannot be a lactone. It must therefore be represented as the acetate of an oxide, $C_{30}H_{44}O_4$ (IV) or (V), the latter being favoured by the Swiss authors.

Kon's formulation (III) of (*C*) would similarly give rise to (VII) or (VIII) for (*J*), and to (IX) for the pyridazine derivative. The absorption spectrum of (*J*) is in better agreement (see Fig. 1, also Ruzicka, Müller, and Schellenberg, *loc. cit.*) with (V) and (VIII) than with either (IV) or (VII). A much more decisive discrimination between these alternatives, however, is provided by the absorption spectrum (Fig. 2) of the acid (*N*), $C_{30}H_{46}O_5$, to which the keto-oxide (*K*) gives rise on energetic hydrolysis. Jacobs and Fleck (*loc. cit.*) found that (*K*) was unaffected when boiled with 2N-alcoholic potassium hydroxide or when heated with 5% alcoholic alkali at 130°, but was hydrolysed if the concentration of the alkali in the latter case was 10%. Ruzicka and Jeger (*loc. cit.*, 1942) have also prepared the acid, but found that more drastic conditions (10% methyl-alcoholic alkali at 200—210°) were required than those given by the American workers. We ourselves obtained the acid some three years ago by the convenient method of gentle refluxing with 2½% sodium amyloxide.

The properties of this acid, which was not studied by Jacobs and Fleck, are very characteristic; in contrast to the parent keto-oxide, it is very sensitive towards oxidising agents, and is slowly affected even by the atmosphere. It has a pronounced yellow colour, gives an intense ferric reaction in alcohol and a yellow colour with tetranitromethane [(*J*) does not give either of these colour reactions], and shows strong and unusual absorption in the ultra-violet (Fig. 2). All these properties are closely simulated by the related *acetyl methyl* ester (*O*),

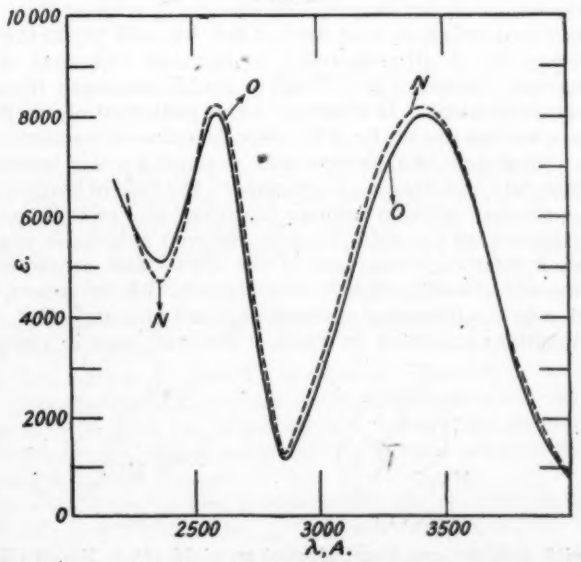
FIG. 1.



which yields unworkable resins on treatment with acetic acid solutions of chromic anhydride (instantaneous oxidation at room temperature), and warm hydrogen peroxide and lead tetra-acetate; the ester contains one active hydrogen atom (Zerewitinoff determination).

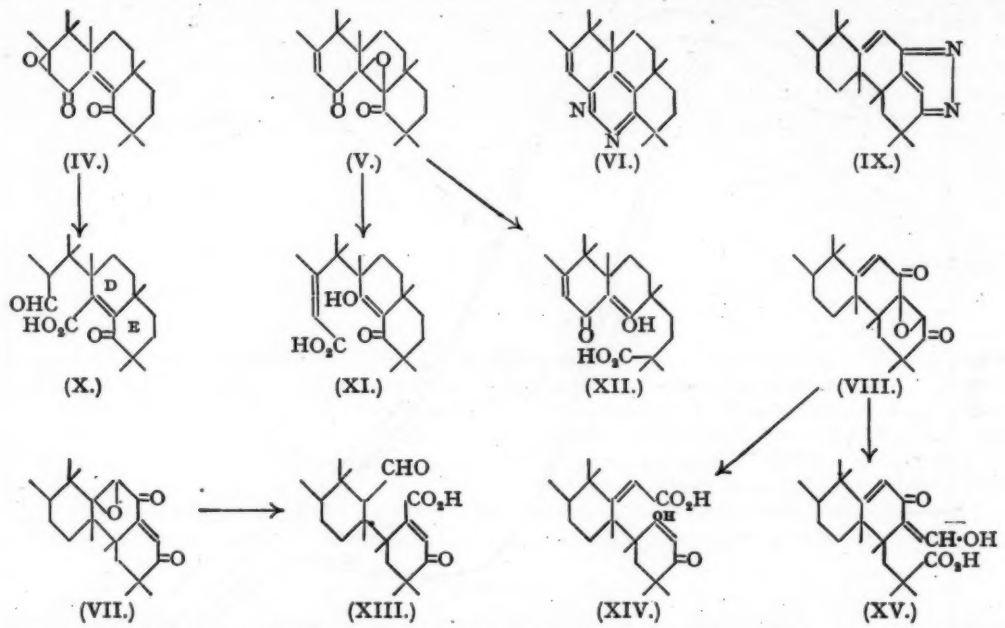
Ruzicka and Jeger also recorded the above colour and colour reactions for this acid and state that it contains three active hydrogen atoms; further, they attributed a change in absorption spectrum on keeping to an enol ⟶ keto conversion. This may well be a contributory factor in the remarkable change, but we believe that atmospheric oxidation is also involved, as old samples of the acid and its acetyl methyl ester (*O*) both gave significantly low carbon values on combustion, and their m. p.'s had also fallen appreciably.

FIG. 2.



Now the three possible structures for the acid (*N*) which can be derived from (IV) and (V) are (X), (XI), and (XII); but since (X) does not account for the ferric reaction shown by (*N*) and (*O*), it must be rejected. Structures (XI) and (XII), on the other hand, are both enolised β-diketones, thus accounting for the ferric reaction, but the conjugation depicted in (XI) is inadequate to account for the absorption spectra of (*N*) and (*O*). The chromophore of (XII), which is the formula advocated by Ruzicka and Jeger, is similar to that of ethyl α-mesityloxidoxalate, $Me_2C{:}CH{\cdot}CO{\cdot}CH{:}C(OH){\cdot}CO_2Et$ (Morton, Hassan, and Calloway, J., 1934, 898), which, in presence of excess sodium ethoxide, shows maxima at 2495, 2870, and 3510 A. (ε = 7500, 7500, and 13,000, respectively).

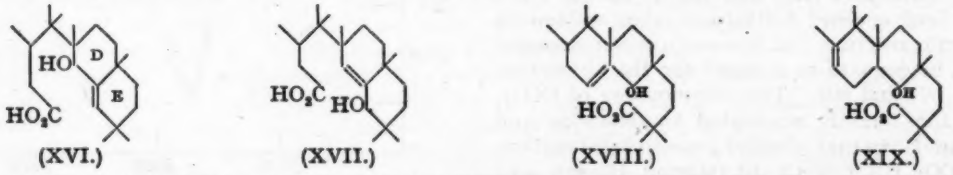
Thus there is at least good qualitative agreement at *ca.* 2500—2600 and at 3500 A. between this compound and the substances (*N*) and (*O*). In the absence of sodium ethoxide, however, the absorption spectrum of



ethyl α-mesityloxidoxalate is markedly different ($\lambda_{max.}$ at 3120 A., $\varepsilon = 14{,}000$); this may of course be due to an enol-keto change, but, if this is so, then Ruzicka and Jeger's suggestion that (*N*) changes into the keto-form on keeping is probably incorrect, as the maxima given by these authors for an old specimen of (*N*) are at 2350 and 3400 A. ($\log \varepsilon = 4{\cdot}05$ and 3·0, respectively). These optical discrepancies cannot perhaps be considered seriously to militate against (XII) as a representation of (*N*), but this structure fails to account for a number of other observations discussed below.

First, we have found that the acetyl methyl ester (*O*) can be readily reconverted into the acid (*N*) by means of 0·3N-alcoholic alkali under reflux. Although the activating effect of carbonyl groups and ethylenic linkages on the alkaline hydrolysis of esters is often not predictable, it is extremely unlikely that the substitution shown in the γ-position of an αα-dimethylbutyric ester (XII) could facilitate hydrolysis to such an extent as actually occurs with the ester (*O*)

Secondly, an argument against the structure (XII) for the acid (*N*) is provided by the properties of the unsaturated dihydroxy-monobasic acid, $C_{30}H_{50}O_4$ (*P*), previously obtained by one of us (J., 1938, 1313) by reduction of the acetoxy-compound (*J*) with sodium and amyl alcohol. Various expressions, which need not be detailed, can be derived for this acid (*P*) on the basis of (IV) and (V), but in each of them the carboxyl group will in all probability be identical with that of the acid (*N*), and this carboxyl evidently cannot be tertiary, because the acid (*P*) is readily produced from its diacetyl methyl ester (*Q*) by boiling it with 0·3N-alcoholic alkali. In contrast to this facile hydrolysis, Bryant and Smith (*J. Amer. Chem. Soc.*, 1936, **58**, 1014), in a systematic study of the saponification of numerous esters, found that ethyl pivalate, the simplest case of an ethyl ester of a tertiary acid, requires 2 hours' heating at 100° under pressure with 2N-methanolic alkali for complete hydrolysis. Furthermore, the ease of hydrolysis of (*Q*) cannot be ascribed to any activating influence on the part of the remaining functional groups in the molecule, for this substance is optically transparent, and oxidation of the acid (*P*) with chromic anhydride yields a ***diketo-acid***, $C_{30}H_{46}O_4$ (*V*), which shows only the weak selective absorption in the ultra-violet characteristic of unconjugated carbonyl groups (Fig. 3). The absence of conjugation in this diketo-acid is important, because it effectively counters the only possible objection to the foregoing argument against formula (XII), *viz.*, that ring-fission of (*J*) may occur in two different directions according to whether this substance is hydrolysed with sodium amyloxide to give (*N*), or reduced



with sodium and amyl alcohol to yield (*P*). For if (XII) were correct, and (*P*) were assumed to arise by a different ring-scission (of ring C), the only two possible structures for (*P*) would be (XVI) and (XVII). In

each of these, the position of the double bond with respect to the hydroxyl group is fixed by the adjacent angle methyl groups, and αβ-unsaturated ketones would therefore result on oxidation, whereas, as already mentioned, an unconjugated product is actually obtained.

Turning now to Kon's formula, (*J*) will be represented by (VII) or (VIII), and (*N*) by (XIII), (XIV), or (XV), and each of the last three is open to the same objections as (X), (XI), and (XII), respectively; *i.e.*, (XIII) would not give a ferric reaction, (XIV) is inadmissible on optical grounds, and (XV) fails to account for the facile hydrolysis of (*O*) and (*Q*) and for the absence of conjugation in the diketo-acid (*V*).

The diacetyl methyl ester (*Q*) gives an *oxide*, $C_{35}H_{56}O_7$ (*R*), on treatment with perbenzoic acid; oxidation with chromic anhydride, on the other hand, yields an *isomer* (*S*), which shows the weak absorption (Fig. 3) indicative of an isolated carbonyl group. The same product (*S*) is obtainable from the acid (*P*) by the alternative route of acetylation, oxidation, and methylation; the oxidation product (*U*) of the diacetyl acid (*T*) showed an absorption spectrum (Fig. 3) indicating the presence of about 20% of an αβ-unsaturated ketone as contaminant, which was removed by methylation and recrystallisation of the mixture. The double bond in the

FIG. 3.

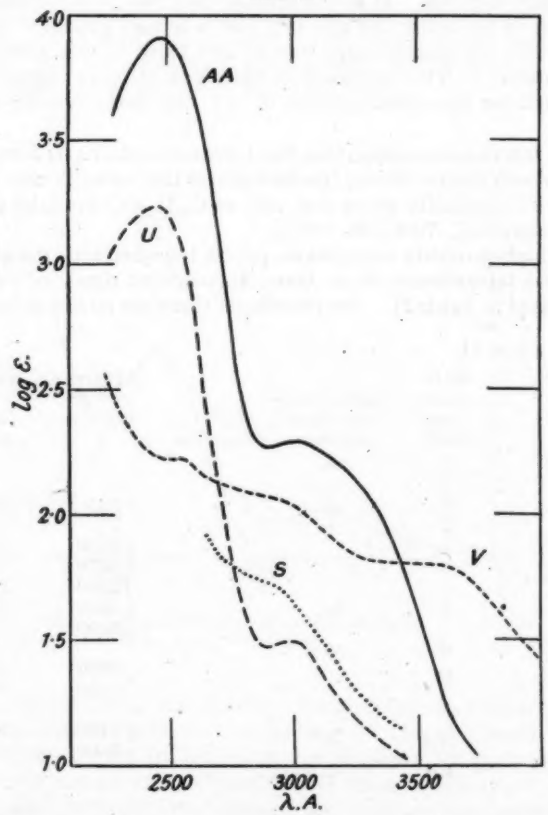
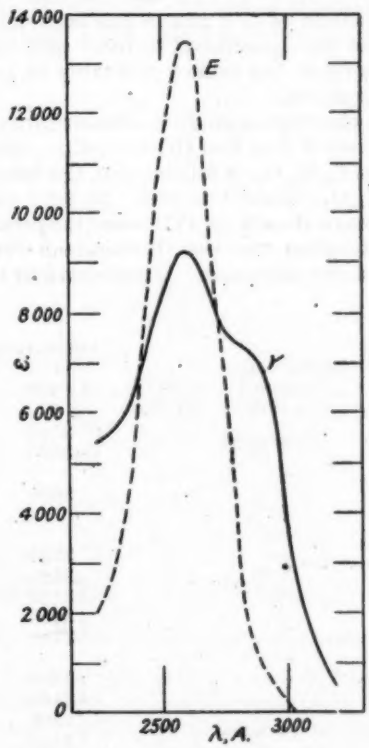


FIG. 4.



acid (*P*) thus appears to undergo two simultaneous types of oxidation, *viz.*, $>C{:}CH{\cdot}CH_2^- \longrightarrow >CH{\cdot}CO{\cdot}CH_2^-$ (mainly) and $>C{:}CH{\cdot}CO^-$, as so often occurs with the natural triterpene acids and alcohols. The position of the main band (2450 A.) of the absorption curve of (*U*) is fully in harmony with the view that the double bond of (*P*) is susceptible to this bi-directional oxidation, for it indicates that the αβ-unsaturated ketone, formed as the minor product, is of the disubstituted type $\begin{matrix}a\\b\end{matrix}\!>\!C{=}CH{\cdot}CO^-$ (*Ann. Reports*, 1941, **38**, 18). It may be noted that, of all the formulations of (*P*) derivable from (V) and (VIII), only two, (XVIII) and (XIX), fulfil this condition, and these are excluded for reasons already given.

The foregoing considerations lead to the conclusion that neither (I) nor (III) is a correct representation of the hydroxy-dione (*F*). We regard the inadequacy of these structures to explain our observations as due, not to the actual nature of the chromophore—the experiments of Ruzicka and Jeger (*loc. cit.*, 1941) would seem to be quite conclusive on this point—but rather to the fact that the chromophore is incorrectly sited either in the molecule as a whole or with reference to neighbouring angle methyl groups.

A further difficulty, which gives additional substance to these conclusions, is experienced when one attempts to formulate, on the basis of (I) or (III), the lactone (*Y*), to which the formula $C_{28}H_{38}O_4$ was ascribed in Part V (J., 1939, 755). This lactone is obtained in small amount when the substance (*K*), $C_{30}H_{44}O_4$, is oxidised with chromic anhydride in presence of sulphuric acid. [*] Six analyses by two analysts (A. Schoeller and W. F. Boston)

have now been carried out on three different samples of the lactone, and have given, as extreme values, C, 76·52, 76·10 (mean 76·34); H, 8·79, 8·49 (mean 8·64%), the means agreeing more closely with the values (76·66 and 8·74%) required by $C_{28}H_{38}O_4$ than with any other formula; this formula is also supported by analytical data obtained for the monobasic *acid* (*Z*) and the methyl ester (*AA*) previously described (*loc. cit.*). Unfortunately, this lactone is not available in quantity, many experiments having failed to improve the yield, which in no case exceeds 10% of the precursor (*K*); hence, it has not yet been possible to characterise the two remaining oxygen atoms, but the following points have been established.

Hydrolysis of (*Y*) with 12% alcoholic potassium hydroxide and also with 2½% sodium amyloxide gives the same product (*Z*). This hydrolysis, in sharp contrast to that of (*J*), produces no radical change of chromophore, as may be seen by comparing the absorption spectrum of (*Y*) with that of the related ester (*AA*) (Figs. 4 and 3 respectively); correspondingly, neither this ester nor the related acid (*Z*) gives a coloration with ferric chloride, in contrast to substances (*O*) and (*N*). The esters (*AA*) and (*O*), however, resemble each other in the ease with which they undergo alkaline hydrolysis to the parent acids. The ester (*AA*) does not react with acetic anhydride in pyridine at 100° or with semicarbazide acetate in boiling alcohol; the lactone (*Y*) is likewise unaffected by semicarbazide and phenylhydrazine acetates. It is not certain that the carboxyl liberated in the hydrolysis of (*Y*) is identical with that present in the acids (*N*) and (*P*), but it is very probable that, in the formation of (*Y*), ring A has been oxidised beyond the ketone stage (we do not know of any instance of failure of the C_2-carbonyl to react with ketonic reagents). The implications arising from these observations are important, but cannot profitably be pursued until the functional groups of (*Y*), (*Z*), and (*AA*) have been fully diagnosed.

The dimethyl ester (*BB*), obtained from the acid fraction accompanying the formation of (*Y*), is formed by the rupture of ring A of (*K*) at C_2–C_3. Since, as has been shown above, the formula of the latter is now established as $C_{30}H_{44}O_4$, it follows that the formula of (*BB*), originally given (*loc. cit.*) as $C_{32}H_{44}O_7$, must be revised to $C_{32}H_{46}O_7$ (Found: C, 70·9; H, 8·5. $C_{32}H_{46}O_7$ requires C, 70·8; H, 8·6%).

We have already (p. 477) noted the persistence of high-intensity absorption spectra together with the absence of unsaturation reactions (Liebermann–Burchard and tetranitromethane tests) throughout many of the substances under discussion. This behaviour is summarised in Table II. On the whole, there are no inconsistencies

TABLE II.

Substance (see chart).	Liebermann–Burchard reaction.	$C(NO_2)_4$ reaction.	Absorption spectra. λ, max., A.	Absorption spectra. log ε, max.	Substance (see chart).	Liebermann–Burchard reaction.	$C(NO_2)_4$ reaction.	Absorption spectra. λ, max., A.	Absorption spectra. log ε, max.
C	+ weak	−	2740 ~3600	4·05 1·95	*Q*	+	+		
D	+	−			*R*	+	−		
E	+	−	2600	4·13	*S*	+	−	~2850	1·75
F	+	−			*T*	+	+		
G	−	−			*U*			2450 2970	3·24 1·50
H	−	−	2735	3·94				2390	2·27
J	+ weak	−	2585 3480	4·07 1·83	*V*	+	+	2530 3550	2·22 1·85
K	+	−	2585 3465	4·11 1·80	*W*	+	+		
L	−	−			*Y*	−	−	2600 2820	3·96 3·87
M	−	−	2550 3160	3·99 2·47	*Z*	−	−		
N	+ weak	+	2600 3430	3·92 3·92	*AA*	−	−	2480 3000	3·90 2·295
O	+ weak	+	2590 3465	3·91 3·91	*BB*	+ weak	−		
P	+	doubtful							

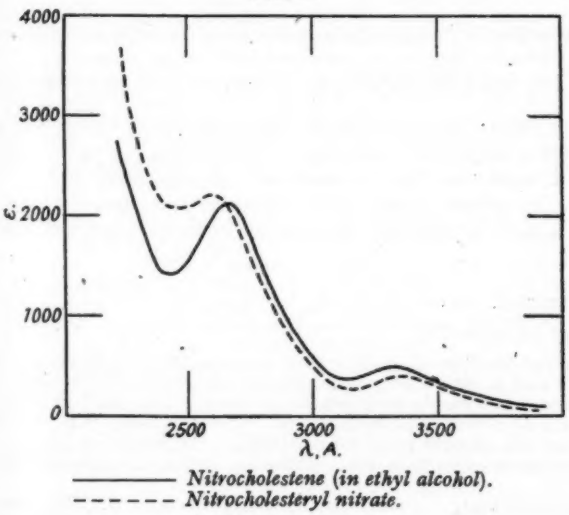
between the actual responses to the tetranitromethane test and those that might be expected on the basis of the types of chromophore present, in so far as these are known. Thus, the acid (*P*) is the parent compound of a group of substances of which the majority give positive tetranitromethane reactions. It has already been shown that (*P*) contains an isolated double bond, and, apart from the abnormally weak response of the acid itself, there is nothing unusual in the behaviour of its congeners in the tetranitromethane test. With the exception of this group of compounds, there are only three instances of positive tetranitromethane reactions in Table II, *viz.*, (*N*), (*O*), and (*W*). Of these, (*W*), from its mode of formation, obviously contains an isolated double bond which has been introduced by the well-known dehydrating action of phosphorus pentachloride on triterpene derivatives hydroxylated at C_2 (compare Vesterberg, *Ber.*, 1887, **20**, 1247; Nöjd, *Arch. Pharm.*, 1927, **265**, 381; Winterstein and Stein, *Annalen*, 1933, **502**, 223), while in (*N*) and (*O*) the chromophore of (*J*) has been radically changed, as has been shown above. The nature of the chromophore in the series (*Y*), (*Z*), and (*AA*) cannot yet be deduced with certainty, so no comment on their negative tetranitromethane reactions in relation to structure can be made, apart from the obvious inference that isolated ethylenic linkages are absent.

Examination of the data in Table II on the Liebermann–Burchard reaction, in conjunction with the chart, shows that these data can be rationally interpreted on the basis of Ruzicka and Jeger's chromophore for (*C*)

by making two postulations, *viz.*, (i) that, in polycyclic hydroaromatic compounds, conjugated systems other than those composed of a pair of ethylenic linkages give negative Liebermann–Burchard reactions; and (ii) that triterpene derivatives containing a hydroxyl or an acetoxyl group attached to C_3 give positive Liebermann–Burchard reactions irrespective of the structure of the remainder of the molecule.

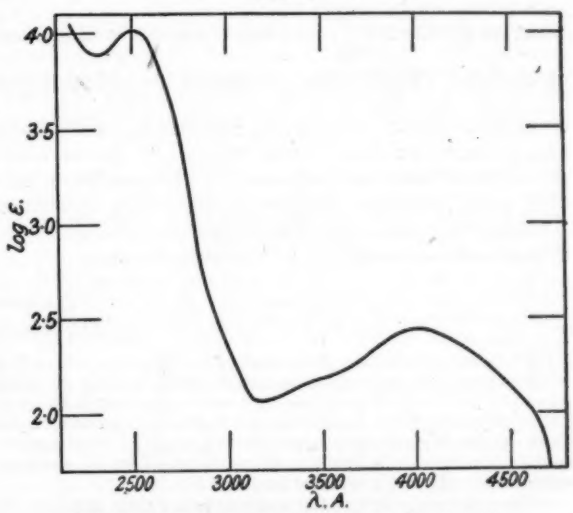
Ruzicka, Goldberg, and Wirz (*Helv. Chim. Acta*, 1935, **18**, 61) state that the saturated triterpene alcohols dihydrobetulin and dihydrolupeol give positive responses in the Liebermann–Burchard test, but the validity of this observation *per se* as evidence for (ii) is discounted by the well-known difficulty of removing the final traces of unsaturated precursors during catalytic reductions. However, a comparison of the acetoxy- and hydroxy-diones (*C*) and (*F*) with the triketone (*G*), and of the acetoxy- and hydroxy-compounds (*J*) and (*K*) with the corresponding ketone (*L*), leaves no room for doubt that acetoxyl and hydroxyl groups attached to C_3 give rise to centres of unsaturation in this reaction. Similarly, each member of the series (*Y*), (*Z*), and (*AA*), in which the hydroxyl in ring A has been removed by oxidation, gives a negative reaction. The ready removal of the elements of water (or acetic acid) from the hydroxylated (or acetoxylated) ring A in the Liebermann–Burchard reaction is obviously comparable with the facile dehydration by means of phosphorus pentachloride already referred to. This instability in acid media is peculiar to the triterpene type of molecule among polycyclic hydroaromatic compounds; in the sterol group, on the other hand, it is well established that saturated members give negative Liebermann–Burchard reactions, and that they react normally with phosphorus pentachloride to yield the saturated chlorides.

FIG. 5.



——— *Nitrocholestene (in ethyl alcohol).*
– – – – – *Nitrocholesteryl nitrate.*

FIG. 6.

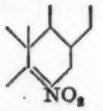
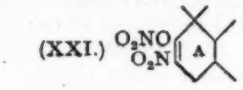
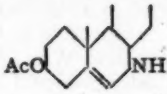


Windaus's compound, $C_{27}H_{41}O_6N_3$, in alcohol.

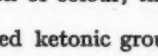
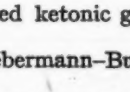
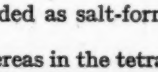
Having regard to the negative Liebermann–Burchard reactions shown by (*G*), (*L*), (*Y*), (*Z*), and (*AA*), to what has already been said respecting the chromophores in these substances, and to the absorption spectra exhibited by these chromophores, the necessity for postulate (i) is self-evident. The generalisation expressed therein has not previously been made either in the sterol or in the triterpene series; indeed, before we were convinced of its truth, we regarded the negative reactions of the substances named as being explicable only on the assumption that these compounds contained an aromatic ring. It will be noted that the nitro-compounds (*H*) and (*M*) also give negative Liebermann–Burchard reactions, and in this connexion we were led to examine nitro-derivatives of the cholesterol series. Although compounds such as nitrocholestene and nitrocholesteryl nitrate have always been represented as unsaturated (XX), the evidence for this does not appear to be entirely conclusive, as it rests largely on the analogy between their reduction to 6-cholestanones and that of nitroindene to β-hydrindone (cf. *Ann. Reports*, 1927, **24**, 131). We have examined the behaviour of nitrocholestene, nitrocholesteryl nitrate, and the compound $C_{27}H_{41}O_6N_3$ [prepared by Windaus (*Ber.*, 1906, **39**, 518) by the action of hot nitric acid on either cholesterol or cholestenone] in the tetranitromethane and the Liebermann–Burchard reaction, and find that all three substances show negative responses; furthermore, nitrocholestene fails to react with perbenzoic acid under the usual conditions. On the other hand, the presence of an isolated (*i.e.*, unconjugated) nitro-group in nitrocholestene and in nitrocholesteryl nitrate is effectively ruled out by their absorption spectra (Fig. 5), which demonstrate conclusively that these substances contain conjugated systems, as represented by (XX); their negative unsaturation reactions are therefore legitimate evidence in favour of the generalisation (i) given above. The constitution of Windaus's compound $C_{27}H_{41}O_6N_3$ is not known; * spectrographically (Fig. 6) it resembles rather strikingly the nitro-compound (*H*) (Fig. 1), but this

* A further point of resemblance between these substances is that each of them—as we have confirmed in the case of $C_{27}H_{41}O_6N_3$—arises by treatment of either the alcohol or the ketone with nitric acid, suggesting the presence of the grouping $O_2NO{\cdot}\overset{|}{C}{=}\overset{|}{C}{\cdot}NO_2$.

may be fortuitous, as the major chromophore in (*H*) appears to be the nitrogen-free system characteristic of (*C*) and (*F*). From analogy with nitrocholestene and nitrocholesteryl nitrate, substances (*H*) and (*M*) are

(XX.)  (XXI.)   (XXII.)

formulated as unsaturated derivatives (XXI), but neither the spectrographic (Fig. 1) nor the analytical data are decisive on this point, although the latter are in better agreement with the H_{40} (unsaturated) than with the H_{42} formulæ [For (*H*): $C_{30}H_{40}O_7N_2$ requires C, 66·64; H, 7·46. $C_{30}H_{42}O_7N_2$ requires C, 66·39; H, 7·80. Found (mean of six analyses): C, 66·72; H, 7·56. For (*M*): $C_{30}H_{40}O_8N_2$ requires C, 64·71; H, 7·24. $C_{30}H_{42}O_8N_2$ requires C, 64·49; H, 7·58. Found (mean of three analyses): C, 65·15; H, 7·57%].

Finally, Eckhardt (*Ber.*, 1938, **71**, 461) states that 7-acetamidocholesteryl acetate (XXII) gives negative responses to both the above colour tests for unsaturation (we are grateful to Dr. E. R. H. Jones for bringing this statement to our notice); here there is no conjugation, and superficially this observation seems to be without parallel. If, however, the assumption is made that, in conjugated systems (C=C—C=O, C=C—NO_2) which cannot be diagnosed by these reactions, a more or less large electromeric shift in the direction of the hetero-atom is vital to the non-production of colour, then the behaviour of (XXII) becomes understandable. For it is known that the αβ-unsaturated ketonic grouping reacts as  , and —C=C·NO_2 will tend to react as  . In the Liebermann–Burchard reaction (concentrated sulphuric acid–acetic anhydride–chloroform) (XXII) may be regarded as salt-forming, *i.e.*, >C:CH·CH_2·$\overset{+}{N}H_2$Ac, which will bring about the condition  (*a*); whereas in the tetranitromethane reaction the grouping NHAc is in the presence of a powerful oxidising agent, which will therefore be highly kationoid with respect to the nitrogen atom with its unshared electron pair, so that the condition (*a*) will again tend to be attained. On the other hand, in conjugated *ethylenic* linkages in polycyclic hydroaromatic systems there is normally no tendency for such "unilateral" electronic displacements; the electromeric shift is therefore far smaller in magnitude, and the system behaves normally in unsaturation tests.

Experimental.

(Melting points are uncorrected.)

Reduction of Acetoxy-compound (*J*).—The compound (2 g.) was dissolved in boiling amyl alcohol (100 c.c.) and treated with sodium (10 g.), added in small pieces during 80 mins. (more rapidly towards the end of the reaction); a further quantity (50 c.c.) of amyl alcohol was added after the reaction had been in progress for 70 mins. The solution, after being refluxed for a total time of 2 hours, was decomposed with water while still warm. The amyl-alcoholic layers from six such reductions were united, washed with water, and the alcohol removed in steam. The resultant aqueous suspension was shaken with two portions of ether, and the emulsions separated by centrifuging into a sparingly-soluble sodium salt (i) and a neutral fraction (ii).

The ethereal solution (ii) was washed, dried, and evaporated, yielding a residue which rapidly crystallised. The product, which was very sparingly soluble in ether, separated from acetone–methanol in brittle, glassy rods (0·65 g.), which frothed at 135—150° and gave a clear melt at 210—220°, unchanged by further crystallisation. Acetylation of this substance (pyridine–acetic anhydride) gave a product which crystallised from acetone or acetone–methanol in well-formed, prismatic needles, m. p. 195—205° to a paste which cleared at about 250°. The *substance* gave an intense brownish-yellow colour with tetranitromethane in chloroform (Found: C, 78·9; H, 10·5. $C_{26}H_{40}O_3$ requires C, 78·9; H, 10·6%).

Fraction (i) on acidification with acetic acid and extraction with ether yielded the acid (*P*), somewhat sparingly soluble in acetone; it formed flat prisms from methyl alcohol, m. p. 264·5—265·5°. The specific rotation could not be determined in chloroform owing to the low solubility of the acid, or in pyridine because the purest solvent available absorbed yellow light. The diacetyl methyl ester (*Q*), obtained as previously described, was sparingly soluble in methyl alcohol, and crystallised from acetone–methyl alcohol in long flat needles, m. p. 228—229°, $[\alpha]_D^{16°}$ + 63° (l = 1, c = 3·22 in chloroform) (Found: 73·4; H, 9·9. Calc. for $C_{35}H_{56}O_6$: C, 73·4; H, 9·8%). The pure diacetyl ester was also readily prepared from the crude acid [total yield from 12 g. of (*J*), 2·7 g.].

Diacetyl Methyl Ester Oxide (*R*).—The ester (*Q*) (60 mg.) was dissolved in a chloroform solution of perbenzoic acid (5 c.c. of 0·3N) and kept at 0°. After 11 days the solution and accompanying blank were titrated with 0·1N-thiosulphate (Found: 3·15 c.c. Calc.: 2·10 c.c.). The *oxide*, isolated in the usual manner, separated from acetone in sheaves of fine needles, m. p. 233·5—234·5° (Found: C, 71·5; H, 9·6. $C_{35}H_{56}O_7$ requires C, 71·4; H, 9·6%).

Quantitative Saponification of Diacetyl Methyl Ester (*Q*).—0·4624 G. of the ester was refluxed for 4½ hours with 30 c.c. of 0·3477N-alcoholic potassium hydroxide, and the solution and blank then back-titrated with standard acid (phenolphthalein) (Found: 6·73 c.c. Calc. for $C_{35}H_{56}O_6$, 3 equivs.: 6·97 c.c.). The solution was acidified with acetic acid, and the regenerated acid precipitated with water. After crystallisation from methyl alcohol and then from acetone, it had m. p. 262·5—264° (0·3 g.), undepressed by admixture with an authentic specimen. The ester was also hydrolysed to some extent (1·70 equivs.) after being refluxed for 2½ hours with 6 equivs. of 0·1N-alcoholic alkali; the solution obtained after back-titration was treated with more alcoholic alkali to give a *ca.* 0·05N-solution (400% excess) and refluxed for a further 18 hours, which resulted in a total consumption of 2·73 equivs. The reluctance to undergo complete hydrolysis in the presence of 0·1N, or weaker, alkali may be due either to the carbomethoxyl or to the acetoxyl group.

Diacetyl Acid (*T*).—500 Mg. of the acid (*P*) were dissolved in pyridine (3 c.c.) and heated for 2½ hours on the steam-bath with acetic anhydride (2 c.c.). The *diacetate*, obtained by precipitation with water, crystallised from aqueous acetone in prisms, m. p. 249—251° after shrinking at 232°, $[\alpha]_D^{15°}$ + 59° (l = 1, c = 2·565 in chloroform) (Found: C, 72·5; H, 10·0. $C_{34}H_{54}O_6$ requires C, 73·1; H, 9·8%).

Oxidation of Diacetyl Acid.—A solution of the acid (*T*) (500 mg.) in glacial acetic acid (20 c.c.) was treated during 45 mins. at 60—65° with a solution of chromic anhydride (200 mg.) in water (2 c.c.) and acetic acid (10 c.c.). After a further ½ hour, methyl alcohol was added, most of the solvent removed under reduced pressure, and the residue treated with water and extracted with ether–chloroform. The extract was washed with water, 2% sodium hydroxide solution, and again with water. The dried ethereal extract gave no residue on evaporation. Acidification of the alkaline fraction with hydrochloric acid gave the *acid* (*U*), which separated from aqueous acetic acid, aqueous methanol, or aqueous acetone in thin laminæ, m. p. 285—286° after shrinking at 253°. A preparation of the same m. p. was also obtained from another experiment in which the oxidation product was simply precipitated with water and recrystallised; the m. p. was also unchanged after treatment of the acid with pyridine and acetic anhydride [Found (two preparations): C, 71·1, 71·0; H, 9·6, 9·4. $C_{34}H_{54}O_7$ requires C, 71·0; H, 9·5%. $C_{34}H_{52}O_7$ requires C, 71·3; H, 9·2%].

Diacetyl Keto-dihydro Methyl Ester (*S*).—(*a*) Treatment of the foregoing acid with ethereal diazomethane gave a crude product which formed prismatic needles, m. p. 261—264°, from acetone–methanol. Continued recrystallisation yielded the *ester* (*S*) as irregular plates, m. p. 275—277° (Found: C, 71·8; H, 9·8. $C_{35}H_{56}O_7$ requires C, 71·4; H, 9·6%).

(*b*) A solution of the ester (*Q*) (500 mg.) in glacial acetic acid (20 c.c.) was treated with one of chromic anhydride (200 mg.) in water (2 c.c.) and acetic acid (10 c.c.), added during 30—35 mins. at 70—72°. After a further 40 mins., water was added, and the resultant precipitate crystallised repeatedly from acetone–methanol. The product had m. p. 275—277° and gave no depression in m. p. when mixed with the sample obtained by method (*a*).

Diketo-acid (*V*).—A solution of chromic anhydride (80 mg.) in water (1 c.c.) and glacial acetic acid (1 c.c.) was added in one portion to one of the acid (*P*) (180 mg.) in acetic acid (14 c.c.) and water (3 c.c.). After 72 hours at room temperature, water was added, and the filtered and washed *keto-acid* (*V*) recrystallised several times from aqueous alcohol, from which it separated in soft needles, m. p. 192—194° after slight previous sintering, extremely soluble in acetone, methyl and ethyl alcohol, and ethyl acetate (Found: C, 76·7; H, 9·9. $C_{30}H_{44}O_4$ requires C, 76·5; H, 9·9%).

Preparation of Acid (*N*).—To a cold solution of sodium (5 g.) in amyl alcohol (100 c.c.) were added 5 g. of the acetoxy-compound (*J*) and 100 c.c. of amyl alcohol. The whole was refluxed for 1½ hours, the originally clear yellow solution rapidly becoming turbid. The sodium amyloxide was decomposed with water, the amyl alcohol removed in steam, and the aqueous suspension of non-volatile residue extracted twice with ether. Evaporation of the dried ethereal solution gave about 0·5 g. of a partly crystalline residue, which was not identical with (*K*) but has not been further examined. The aqueous fraction, freed from neutral material, was acidified with acetic acid and extracted with ether. Evaporation of the washed and dried solution furnished a crystalline residue, which was recrystallised from aqueous alcohol or acetone. The freshly-prepared acid formed brittle yellow prisms, m. p. 240—241° after sintering at 237°, but the m. p. of a sample which had been kept for some months was only 229—234°. An alcoholic solution of the acid gave a deep greenish-blue colour with ferric chloride [Found (old sample): C, 73·2; H, 9·5; (freshly-prepared sample): C, 73·9; H, 9·5. Calc. for $C_{30}H_{46}O_5$: C, 74·0; H, 9·5%].

Acetyl Methyl Ester (*O*).—Treatment of the above acid with diazomethane in ether–acetone yielded the methyl ester, which crystallised from aqueous methanol in heavy transparent prisms, m. p. 130—145°, apparently containing solvent of crystallisation; one further crystallisation from benzene–ligroin furnished hard yellow rosettes of prismatic needles, m. p. 149—151°. This ester (1 part) was heated at 100° for 2—3 hours with pyridine (3 parts) and acetic anhydride (2 parts). Addition of water precipitated the *acetyl* derivative (*O*), which crystallised from slightly aqueous alcohol in yellow, soft, pearly plates, m. p. 179—180·5°; on rapid cooling of its solutions, the ester showed a tendency to separate as a gelatinous, hair-like mass. The ferric chloride reaction was similar to that given by the free acid, and, like the latter, the m. p. of a sample of the ester which had been kept for some weeks fell considerably (165—170°) [Found (old sample): C, 72·3; H, 9·1; (freshly-prepared sample): C, 72·7; H, 9·2. $C_{33}H_{50}O_6$ requires C, 73·0; H, 9·3%]. *Active hydrogen determination* (*Zerewitinoff*): 3·767 Mg. gave 0·170 c.c. of methane (762 mm., 21°), corresponding to 1·02 active hydrogen atoms. The ester was recovered unchanged after its alcoholic solution had been refluxed with *o*-phenylenediamine for 5 hours or hydroxylamine hydrochloride and sodium acetate for 12 hours.

In a quantitative saponification, 0·3608 g. of the ester was refluxed for 3 hours with 30 c.c. of 0·3462N-alcoholic potassium hydroxide (Found: 6·47 c.c. $C_{33}H_{50}O_6$ requires 7·04 c.c. for 2 equivs.). The regenerated acid, obtained by acidification with acetic acid, was crystallised from aqueous acetone and then from a small volume of absolute methanol; it had m. p. 240·5—242° after slight previous sintering, and gave no depression when mixed with an authentic sample.

Preparation of Substance, $C_{29}H_{42}O_2$ (*W*).—The compound (*K*) (400 mg.) was added to a suspension of phosphorus pentachloride (250 mg.) in ligroin (7·5 c.c.) (b. p. 40—60°). The mixture was refluxed for 2½ hours and then treated with water and extracted with chloroform. The extract was washed with 2% aqueous sodium hydroxide and with water, dried, and evaporated. The residue was crystallised first from aqueous alcohol and then from acetone, from which the *substance* (*W*) separated in stout rods, m. p. 295—297° (decomp.), largely depressed on admixture with the original hydroxy-compound. The Beilstein reaction was negative (Found: C, 80·2; H, 9·3. $C_{29}H_{42}O_2$ requires C, 79·9; H, 9·4%). In different experiments the m. p. was found to vary slightly with alterations in the quantities of reagent and solvent employed. The use of chloroform instead of ligroin gave an oily product from which only a small quantity of low-melting material (m. p. 220—230°) could be isolated.

Experiments with the Lactone, $C_{28}H_{38}O_4$ (*Y*).—(*a*) In numerous minor variations of the original conditions for the preparation of this compound (J., 1939, 755), the original observation was invariably confirmed that the lactone is isolated from the *acid* fraction of the oxidation products of (*K*). To see whether this might not be due to scission of a labile lactone ring of (*Y*) during the working-up of the product, a solution of (*Y*) in chloroform–ether was shaken with portions of 3% aqueous sodium hydroxide, and subsequently with water. Neither the aqueous nor the alkaline washings gave any precipitate on acidification, and on evaporation of the ether–chloroform solution the lactone was recovered unchanged. Since the acid (*Z*) (*q.v.*) shows no tendency to relactonise, it follows that the appearance of (*Y*) in the acid fraction of the oxidation products of (*K*) must be due, as previously surmised, to a loose association between molecules of it and the mixed acids.

The lactone is very sparingly soluble in ether, moderately soluble in hot methyl and ethyl alcohol, and fairly readily soluble in hot ethyl acetate and acetone. The last three solvents were used in the preparation of samples for analysis.

(*b*) The lactone (200 mg.) was added to a cold solution of sodium (200 mg.) in amyl alcohol (4 c.c.). A further 4 c.c. of amyl alcohol were added, and the mixture heated under reflux for 1½ hours. The solution was decomposed with water while still warm, the amyl alcohol removed in steam, the alkaline solution extracted thrice with ether, and then acidified with acetic acid. The precipitate was isolated by means of ether and crystallised from aqueous acetic acid, yielding the *acid* (*Z*) as a micro-crystalline solid, m. p. 247—252° (160 mg.), very soluble in methyl alcohol, ethyl acetate, and acetic acid. It separated as a gel from ethyl acetate–ligroin, but on recrystallisation from aqueous acetic acid formed opaque nodules of tiny needles, m. p. 251—253° (Found: C, 73·4, 73·55; H, 8·7, 8·9. $C_{28}H_{40}O_5$ requires C, 73·6; H, 8·8%). The acid gave no colour with either neutral or acid ferric chloride in alcoholic solution. Esterification with diazomethane in ether–acetone solution gave the methyl ester (*AA*); this separated from aqueous methanol in plates, m. p. 211·5—213°, and gave no depression in m. p. when mixed with an authentic specimen prepared from (*Y*) by hydrolysis with 2N-alcoholic potassium hydroxide.

The ester did not give a coloration in alcoholic solution with ferric chloride; it was recovered unchanged after being heated with pyridine and acetic anhydride at 100° for 4½ hours, and after 5½ hours' refluxing with semicarbazide acetate in alcohol. Hydrolysis of the ester was readily accomplished by refluxing it for 4½ hours with 0·3N-alcoholic potassium hydroxide; the solution, which gave no precipitate on dilution with water, was extracted with ether and then acidified with acetic acid. The precipitated acid (*Z*), on recrystallisation from acetic acid, formed micro-needles, m. p. 249—252°, and 251—253° on admixture with the specimen described above.

Note on Liebermann–Burchard Tests.—In Table II, a substance which gives a clear yellow, or paler, solution, is considered to show a negative reaction. The conditions used throughout the tests were considerably more drastic than the mild conditions which are sufficient to produce positive reactions with steroids and triterpenes containing isolated ethylenic linkages; the tests were not performed on a strictly quantitative basis, but the general procedure was as follows. 1—2 Mg. of the substance were dissolved in 2—3 drops of chloroform, 3—4 drops of acetic anhydride were added, and then 3—5 drops of concentrated sulphuric acid. A considerable difference in sensitivity was noted between substances containing isolated double bonds, *e.g.*, (*P*), (*Q*), (*W*), and those in which a positive reaction was obtained as a result of dehydration at C_2, *e.g.*, (*C*), (*F*), (*J*), (*K*); the latter compounds gave negative results under the mild conditions (low concentrations of acid and substance relative to chloroform) which produce positive reactions with unsaturated steroids.

One of us (J. C. E. S.) wishes gratefully to acknowledge a research grant from the Council of the Durham Colleges which has facilitated this work.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.
UNIVERSITY OF LIVERPOOL.

[*Received, June 28th,* 1943.]

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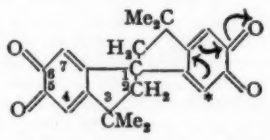
130. *Condensation Products of Phenols and Ketones. Part VI. The Conversion of an o-Quinone into a Derivative of Pyrogallol.*

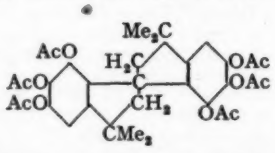
By WILSON BAKER and J. C. MCGOWAN.

The *o*-quinone (I) is converted by acetic anhydride–sulphuric acid into a mixture of hexa-acetoxy-compounds, from which two pyrogallol derivatives, (II) and an *isomer*, have been isolated. This novel result is discussed.

CATECHOL and acetone condense in presence of acetic and hydrochloric acids to give a tetrahydroxy-3 : 3 : 3′ : 3′-tetramethylbis-1 : 1′-*spiro*hydrindene (Baker, J., 1934, 1678; Baker and McGowan, J., 1938, 347), and very strong evidence was brought forward to show that the hydroxyl groups occupied positions 5, 6, 5′, and 6′. Oxidation of this compound with fuming nitric acid in alcohol gives the corresponding red di-*o*-quinone (I) (Baker, *loc. cit.*), and it has now been found that treatment of this quinone with acetic anhydride and a trace of concentrated sulphuric acid gives a mixture of hexa-acetoxy-compounds, one of which is identical with the hexa-acetate (II) of the substance which is obtained by the condensation of pyrogallol with acetone in presence of acetic and hydrochloric acids. The latter substance has already been shown to be a hexahydroxy-3 : 3 : 3′ : 3′-tetramethylbis-1 : 1′-*spiro*hydrindene (Baker and Besly, J., 1939, 196), and the evidence available suggested that the hydroxyl groups were symmetrically arranged and occupied positions 5, 6, 7, 5′, 6′, and 7′.

(I.)





(II.)

That the Thiele acetylation of (I) gives a derivative of pyrogallol rather than of hydroxyquinol is strong evidence that all the reactive cationoid positions para to the oxygen atoms are already substituted, thus confirming the positions previously assigned to the four hydroxyl groups in the catechol–acetone condensation product. It is remarkable, however, that an *o*-quinone should be capable of giving a pyrogallol derivative in this reaction, and it must be assumed that the carbon atoms adjacent to the carbonyl groups may become cationoid owing to the transmission of the electromeric effect through two double bonds of the quinone structure, as shown for one of the reactive positions in (I). Reactions of the Thiele acetylation type have been little investigated with *o*-quinones; β-naphthaquinone yields 1 : 2 : 4-triacetoxynaphthalene (Thiele and Winter, *Annalen*, 1900, **311**, 341).

All four positions 4, 7, 4′, and 7′ in the quinone (I) will probably be almost equally reactive, and as one acetoxyl group is introduced into each aromatic nucleus, three isomeric hexa-acetoxy-compounds should be formed, (II), the 4 : 5 : 6 : 5′ : 6′ : 7′- and the 4 : 5 : 6 : 4′ : 5′ : 6′-isomers, but no evidence is available to show which of the last two structures is to be assigned to the lower-melting, second *isomer* which has been isolated. Owing to molecular asymmetry all the bis-1 : 1′-*spiro*hydrindenes mentioned are racemic forms.

EXPERIMENTAL.

Thiele Acetylation of the Quinone (I).—(a) *Isolation of* 5 : 6 : 7 : 5′ : 6′ : 7′*-hexa-acetoxy-*3 : 3 : 3′ : 3′*-tetramethylbis-*1 : 1′*-*spiro*hydrindene* (II). The quinone (I) (2 g.) (Baker, *loc. cit.*) was dissolved in boiling acetic anhydride (20 c.c.), cooled rapidly with stirring, and to the fine suspension of crystals was added a solution of concentrated sulphuric acid (4 drops) in acetic anhydride (2 c.c.). After 3 hours a brownish-red solution was obtained, and, after 20 hours water (100 c.c.) was added, the mixture shaken, and the pale amber-coloured precipitate (3·6 g.) collected after the hydrolysis of the acetic anhydride. This amorphous product was dissolved in a little ethyl alcohol and the colourless crystalline deposit which separated overnight was collected, washed with alcohol, and recrystallised from alcohol containing a little

acetic acid, and then twice from alcohol, being obtained in almost rectangular plates (0·21 g.), m. p. 245—246° [Found: C, 63·3; H, 5·7; Ac, 41·7. Calc. for $C_{21}H_{18}(OAc)_6$: C, 63·5; H, 5·8; Ac, 41·3%]. The m. p. was unaltered when the substance was mixed with the hexa-acetate of the pyrogallol–acetone condensation product, m. p. 247°, prepared as described by Baker and Besly (*loc. cit.*).

(b) *Isolation of* 4 : 5 : 6 : 4′ : 5′ : 6′ (or 5′ : 6′ : 7′)-*hexa-acetozy*-3 : 3 : 3′ : 3′-*tetramethylbis*-1 : 1′-spiro*hydrindene*. To the first ethyl-alcoholic mother-liquor from the above crystallisation was added an equal volume of methyl alcohol; after 2 days the colourless crystalline deposit (0·75 g.) was collected, and recrystallised from a mixture of methyl and ethyl alcohols, and then three times from ethyl alcohol, being obtained in bunches of radiating needles (0·22 g.), m. p. 200° after softening from *ca.* 195° [Found: C, 63·4; H, 5·8; Ac, 42·4. $C_{21}H_{18}(OAc)_6$ requires C, 63·5; H, 5·8; Ac, 41·3%]. A mixed m. p. with the isomeric hexa-acetate gave an opaque melt at *ca.* 193°, clearing at about 215°.

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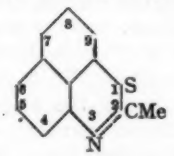
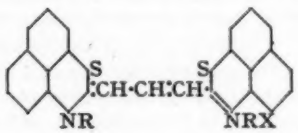
131. *Thiazinocyanines. Part III. Carbocyanines containing the* peri-*Naphtha*-1 : 3-*thiazine Nucleus.*

By FRANCES M. HAMER and RUSSELL J. RATHBONE.

From 2-methyl*peri*naphtha-1 : 3-thiazine, the carbocyanines of Joy and Bogert were obtained free from solvent and an unsubstituted dicarbocyanine was prepared: these dyes are abnormal in being decolorised by alkali. In view of the difficulty of making its quaternary salts, the base itself was condensed with suitable salts, to give the bases of six unsymmetrical carbocyanines. Two carbocyanines were made from one of these. Absorption data for methyl-alcoholic solutions of the dyes are recorded, and comparisons made with the dihydro-1 : 3-thiazine, 2 : 4-benzthiazine, and naphthathiazole series. Styryl compounds also were prepared.

THE preparation of quaternary salts of 2-methylbenzthiazole and of 1-methyl-α-naphthathiazole proceeds smoothly; it is well known that some of the cyanine dyes prepared from these salts are outstandingly valuable photographic sensitisers. By synthesising 2-methyl*peri*naphtha-1 : 3-thiazine (I), Bogert and Bartlett obtained a promising intermediate (*J. Amer. Chem. Soc.*, 1931, **53**, 4046). Joy and Bogert's observation that the new base only with difficulty undergoes quaternary salt formation (*J. Org. Chem.*, 1936, **1**, 236) is interesting because

(I.) 

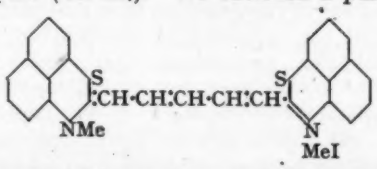


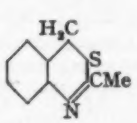
(II.)

so unexpected. They succeeded in making two symmetrical carbocyanines (II; R = Me or Et, X = I) containing the new nucleus, but, unlike the isomeric carbocyanines containing two α- or two β-naphthathiazole nuclei, these were devoid of photographic sensitising action (*loc. cit.*).

In preparing the methiodide of 2-methyl*peri*naphtha-1 : 3-thiazine, we confirmed Joy and Bogert's observation as to the beneficial effect of adding a little quinol, which we added also in preparing the ethiodide. The instability of the methiodide was shown by the drop in yield on recrystallisation. We too were unable to prepare the ethiodide in a state of purity but we prepared a pure specimen of the *hydriodide*. We prepared the two symmetrical carbocyanine iodides (II; R = Me or Et, X = I) by Joy and Bogert's method and confirmed their observation that only short heating can be applied. By modifying their procedure, we succeeded in obtaining both specimens free from solvent, whereas theirs contained chloroform of crystallisation. Starting from the methomethylsulphate of (I), the formation of the *carbocyanine methylsulphate* (II; R = Me, X = SO_4Me) proceeded smoothly, the dye being obtained in 71% yield. Not only were these carbocyanines devoid of sensitising action, but they depressed the original blue sensitivity of the photographic emulsion. A peculiarity is that their alcoholic solutions are reversibly bleached by alkali. In attempts to carry out titrations, sharp end-points were not obtained and it appeared that considerable excess of alkali, over the molecular proportion, was required to effect bleaching.

Joy and Bogert tried to prepare the 12-chloro-derivative of the dicarbocyanine (III) by applying the method of Beattie, Heilbron, and Irving (J., 1932, 260) to 2-methyl*peri*naphtha-1 : 3-thiazine methiodide, but the dye was not obtained pure (*loc. cit.*). We obtained a pure specimen of the unsubstituted dicarbocyanine (III)

(III.) 

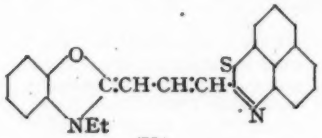


(IV.)

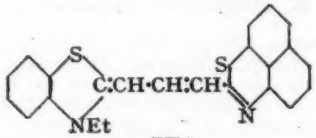
by carrying out its preparation at a low temperature. Its behaviour with alkali resembles that of the carbocyanines (II). Thus its blue chloroform solution was turned yellow by caustic alkali. At first the blue was readily restored by addition of traces of acid or by dilution with methyl alcohol, but, after the chloroform solution had been evaporated to dryness, the brown residue no longer gave a blue colour with acid, indicating

that decomposition had occurred. The bleached dye was free from iodine. Like the carbocyanines (II), the dicarbocyanines (III) did not sensitise but depressed the original blue sensitivity of a photographic plate. The absorption maximum of a methyl-alcoholic solution of the dicarbocyanine (III) is 1100 A. further towards the red than that of the carbocyanine (II; R = Me, X = I).

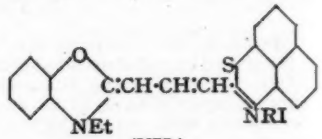
The difficulties which Joy and Bogert experienced in preparing quaternary salts of 2-methyl*peri*naphtha-1 : 3-thiazine (I) (*loc. cit.*) were intensified in the case of the related 3-methyl-2 : 4-benzthiazine (IV), as has been recorded in the first paper of this series (Beilenson and Hamer, J., 1942, 98). However, following the failure to prepare quaternary salts of (IV), it proved possible to condense the base itself with heterocyclic quaternary ammonium salts containing a substituted β-aminovinyl group, cyanine bases thus being obtained, from which carbocyanine dyes could be produced by the action of esters (Beilenson and Hamer, *loc. cit.*). Following this procedure and starting from the base (I), we have now prepared *bases* of unsymmetrical carbocyanines containing the *peri*naphtha-1 : 3-thiazine nucleus. Thus the new base (V) was prepared in 38% yield, by fusing (I) with 2-β-acetanilidovinylbenzoxazole ethiodide, followed by treatment with alkali. Its 4 : 5- and 6 : 7-benz-derivatives were prepared analogously, in 24% and 20% yields. (VI) was prepared in 54% yield and its 4 : 5- and 6 : 7-benz-derivatives in 36% and 35% yields. The *hydrochlorides* of (V) and of the 6 : 7-benz-derivative



(V.)



(VI.)



(VII.)

of (VI) were prepared. By the action of methyl iodide and ethyl iodide, respectively, on (V), two *carbocyanines* (VII; R = Me or Et) were prepared. These new dyes, whether carbocyanines or carbocyanine bases, sensitised weakly and depressed the normal blue sensitivity of the photographic plate.

The six carbocyanine bases of the *peri*naphtha-1 : 3-thiazine series give, in methyl-alcoholic solution, very broad absorption curves, with indefinite maxima. In the 2 : 4-benzthiazine series (Beilenson and Hamer, *loc. cit.*), the carbocyanine bases gave rounded, but much less broad, absorption curves, and the effect of adding acid was to make each curve narrower and the maxima more sharply defined. In the present group, addition of acid has a similar effect; the resultant curves consist of two or more bands, of which the one nearest the red is, in general, the strongest. On passing from the acid salt of (V) to the acid salt of (VI), the absorption maximum shifts 300 A. towards the red end of the spectrum. The effect of introducing the 4 : 5- or 6 : 7-benz-group into the acid salt of (V) or (VI) is to produce a shift of 200 to 250 A. in the same direction. Acid solutions of four unsymmetrical carbocyanine bases containing the 2 : 4-benzthiazine nucleus (*ibid.*, *loc. cit.*) may be compared with those of four in the present series, in which the place of the 2 : 4-benzthiazine nucleus is taken by the *peri*naphtha-1 : 3-thiazine nucleus : this shifts the absorption maximum towards the red, the amount of the shift varying from 100 to 250 A.

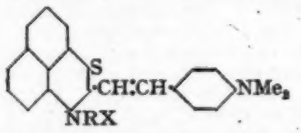
The absorption curves of the carbocyanines (VII; R = Me or Et) are well defined, with the maximum 550 or 600 A. nearer to the red than that of the base (V) and only 50 or 100 A. nearer to the blue than that of the acidified solution of (V). With the unsymmetrical carbocyanine, replacement of the 2 : 4-benzthiazine nucleus (*ibid.*, *loc. cit.*) by the *peri*naphtha-1 : 3-thiazine nucleus, giving (VII; R = Et), is accompanied by a bathochromic shift of 100 A. Replacement of the dihydro-1 : 3-thiazine nucleus (Hamer and Rathbone, this vol., p. 243) by the *peri*naphtha-1 : 3-thiazine nucleus, giving (VII; R = Me), is accompanied by a bathochromic shift of 450 A.

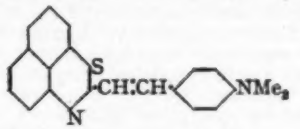
The base (V) has its sensitising maximum in the same position as that of its hydrochloride, methiodide (VII; R = Me) and ethiodide (VII; R = Et); the other dye base and hydrochloride show the same abnormality, which was observed also in the 2 : 4-benzthiazine series (Beilenson and Hamer, *loc. cit.*). As in that series, so also here, the abnormality is considered to lie with the bases and not with the carbocyanines, because with five of the present bases the shift on passing from absorption maximum to sensitising maximum is as much as 900 to 1250 A., whereas with the two carbocyanines it has the more usual values of 350 and 400 A.

As the *peri*naphtha-1 : 3-thiazine nucleus is isomeric with the naphthathiazole nucleus, a comparison of absorption spectra of dyes of these series is of interest. The absorption maxima of the symmetrical thiacarbocyanines, having two α- or two β-naphthathiazole nuclei (Fisher and Hamer, *Proc. Roy. Soc.*, 1936, *A*, **154**, 703) lie 530 and 570 A., respectively, nearer to the red end of the spectrum than that of the thiacarbocyanine having two *peri*naphtha-1 : 3-thiazine nuclei. Those of the symmetrical thiadicarbocyanines having two α- or two β-naphthathiazole nuclei (*idem*, *ibid.*) lie 470 and 510 A., respectively, nearer to the red than that of the thiadicarbocyanine having two *peri*naphtha-1 : 3-thiazine nuclei (here two ethiodides are compared with a methiodide). The absorption maxima of the oxathiacarbocyanines having an α- or β-naphthathiazole nucleus (Beilenson, Fisher, and Hamer, *Proc. Roy. Soc.*, 1937, *A*, **163**, 138) lie 260 and 270 A., respectively, nearer to the red end of the spectrum than that of the oxathiacarbocyanine having a *peri*naphtha-1 : 3-thiazine nucleus.

By condensing the methiodide and the hydriodide, respectively, of (I) with *p*-dimethylaminobenzaldehyde, Joy and Bogert obtained two styryl compounds (VIII; R = Me or H, X = I) (*loc. cit.*). We prepared the corresponding methomethylsulphate (VIII; R = Me, X = SO_4Me) but found that its absorption maximum did not agree with that published for the methiodide. We repeated the preparation of the hydriodide and found

a similar divergence there : the solvent used for the published absorption data has not been recorded. We also prepared the styryl *base* (IX). On acidification of a methyl-alcoholic solution of the base, the absorption

(VIII.) 

 (IX.)

maximum shifted 1260 A. towards the region of longer wave-length. On passing from the base to the hydriodide, and to the methomethylsulphate, the shifts were 1260 and 1350 A., respectively.

Experimental.

8-*Nitronaphthalene*-1-*sulphonyl Chloride*.—In following the directions for nitrating naphthalene-1-sulphonyl chloride (Erdmann and Süvern, *Annalen*, 1893, **275**, 230; Reissert, *Ber.*, 1922, **55**, 858), the yields of 8 : 1-isomer, from its mixture with the 5 : 1-isomer, were variable. The modification of Joy and Bogert (*J. Org. Chem.*, 1936, **1**, 236) was preferred, as the variations were less. Benzene (3 c.c. per g.) was used for the separation, and the resultant yield of 8 : 1-compound, m. p. 149°, was 28%. They obtained a 16% yield, m. p. 154°.

2-*Methyl*peri*naphtha*-1 : 3-*thiazine* (I).—The tin chloride addition compound of 1-thiol-8-acetonaphthalide was prepared from 8-nitronaphthalene-1-sulphonyl chloride, and cyclisation was effected by the method of Bogert and Bartlett (*J. Amer. Chem. Soc.*, 1931, **53**, 4046; cf. Joy and Bogert, *loc. cit.*). The base was recrystallised from spirit (5 c.c. per g.), being obtained in 66% yield, m. p. 93—94°, and base of this quality was used for subsequent work. Recrystallisation from acetone (3 c.c. per g.) brought the m. p. up to 96°, whilst the yield fell to 48%. The substance was dried in a vacuum at 60° and analysed by the method of Carius, which method of analysis was used throughout this work, except where otherwise stated (Found : S, 16·3. Calc. for $C_{12}H_9NS$: S, 16·1%). Bogert and Bartlett record m. p. 96·5—97·5° and their yield, calculated from the same starting point, is 53%.

2-*Methyl*peri*naphtha*-1 : 3-*thiazine Methomethylsulphate*.—2-Methyl*peri*naphtha-1 : 3-thiazine (1·99 g.; 1 mol.) and methyl sulphate (1·4 c.c.; 1·5 mols.), which had been purified by means of sodium bicarbonate and sodium sulphate, were heated together on a steam-bath for 10 minutes. The resultant solid was ground with absolute ether and then with acetone, and was dried in a vacuum desiccator (92% yield), and was used without further purification.

2-*Methyl*peri*naphtha*-1 : 3-*thiazine Methiodide*.—2-Methyl*peri*naphtha-1 : 3-thiazine (3 g.; 1 mol.), methyl iodide (1·2 c.c.; 1·2 mols.), and quinol (0·006 g.) were heated together in a sealed tube at 100°, according to the method of Joy and Bogert (*J. Org. Chem.*, 1936, **1**, 236), but 4 hours was found to be the best time of heating, whereas they heated for 12 hours. Their observation, that addition of quinol has a favourable effect upon the yield, was confirmed by three pairs of comparative experiments. The yield of chloroform-washed product was 60% (2·7 g.) and this was used for subsequent work; Joy and Bogert obtained 62%. After rapid recrystallisation from absolute alcohol (30 c.c. per g.), the yield dropped to 24%. Before analysis, the iodide was dried to constant weight in a vacuum at 60—80°, which method of drying was employed throughout this work, except where otherwise stated (Found : I, 37·0. Calc. for $C_{13}H_{12}NIS$: I, 37·2%). M. p. 177° (decomp.), but Joy and Bogert give m. p. 222—230° (decomp.).

2-*Methyl*peri*naphtha*-1 : 3-*thiazine Ethiodide*.—2-Methyl*peri*naphtha-1 : 3-thiazine (1·99 g.; 1 mol.) and ethyl iodide (1·6 c.c.; 2 mols.) were heated together in a sealed tube at 100°, with addition of quinol (0·006 g.), since Joy and Bogert found this addition useful in the case of the methiodide. The best yield of chloroform-washed product was 40% (1·51 g.) and this was attained by 4 days' heating, whereas they heated for 1 day, without quinol, and got a 39% yield. The yellow powder had m. p. 269—270° (decomp.), with softening from 230°, but the presence of hydriodide was suggested by its acidity to litmus. It was, however, used for preparing the carbocyanine.

2-*Methyl*peri*naphtha*-1 : 3-*thiazine Hydriodide*.—2-Methyl*peri*naphtha-1 : 3-thiazine (1 g.; 1 mol.) was dissolved in hot acetic acid (5 c.c.) and treated with a hot aqueous solution of potassium iodide (3 g.; 3 mols.) in water (5 c.c.). The yield of ether-washed product was 31% (Found : I, 38·7. $C_{13}H_{12}NIS$ requires I, 38·8%). The bright orange crystals had m. p. 260° (decomp.). Joy and Bogert record m. p. 259° (decomp.) for a specimen of hydriodide containing ethiodide.

Bis-2-(3-*methyl*peri*naphtha*-1 : 3-*thiazine*)*trimethincyanine Iodide* (II; R = Me, X = I).—2-Methyl*peri*naphtha-1 : 3-thiazine methiodide (2 g.; 2 mols.), ethyl orthoformate (2 c.c.; 4 mols.), and pyridine (20 c.c.) were boiled together for 4 minutes and the product (0·5 g.; 30% yield) was ground with acetone until the washings were a clean purple. A 28% yield (0·45 g.) of pure dye was thus obtained, m. p. 223° (decomp.) (Found : I, 22·5; S, 11·5. Calc. for $C_{27}H_{21}N_2IS_2$: I, 22·5; S, 11·4%). Its absorption maximum was at 5300 A. Joy and Bogert used half the amount of pyridine and boiled for 5 minutes; by repeated boiling of the filtrate, they obtained more dye and their total yield of washed dye (43%) was higher than ours; we failed to obtain further yields by reheating. After recrystallisation from chloroform, their product, m. p. 221° (decomp.), apparently contained chloroform of crystallisation.

Bis-2-(3-*methyl*peri*naphtha*-1 : 3-*thiazine*)*trimethincyanine Methylsulphate* (II; R = Me, X = SO_4Me).—2-Methyl*peri*naphtha-1 : 3-thiazine methomethylsulphate (2·17 g.; 2 mols.), ethyl orthoformate (4 mols.), and pyridine (10 c.c.) were boiled together for 5 minutes. The purple solution was quickly cooled, and the solid filtered off and washed with ether, being obtained in 71% yield, as green crystals with a golden reflex. M. p. 232° (decomp.). On recrystallising from methyl alcohol (30 c.c. per g.), the yield dropped to 53% but the m. p. was unchanged (Found : S, 17·35. $C_{28}H_{24}O_4N_2S_3$ requires S, 17·5%).

Bis-2-(3-*ethyl*peri*naphtha*-1 : 3-*thiazine*)*trimethincyanine Iodide* (II; R = Et, X = I).—2-Methyl*peri*naphtha-1 : 3-thiazine ethiodide was caused to react with ethyl orthoformate, potassium acetate, and acetic anhydride, and the product was precipitated with ethyl acetate and washed with water, all according to the method of Joy and Bogert (*loc. cit.*), except that 10 times their amount of potassium acetate was used. Instead of boiling out with methyl alcohol, whereby they obtained a 9% yield, we washed exhaustively with ether and thus obtained a pure specimen, free from solvent (Found : I, 21·3. Calc. for $C_{29}H_{25}N_2IS_2$: I, 21·4%), in 10% yield. Its absorption maximum was at 5400 A. M. p. 212° (decomp.). They give m. p. 243° (decomp.) for a sample recrystallised from chloroform and apparently containing solvent of crystallisation.

Bis-2-(3-*methyl*peri*naphtha*-1 : 3-*thiazine*)*pentamethincyanine Iodide* (III).—2-Methyl*peri*naphtha-1 : 3-thiazine methiodide (2·28 g.; 2 mols.), β-anilinoacraldehyde anil hydrochloride (0·86 g.; 1 mol.), anhydrous potassium acetate (2·4 g.; 8 mols.), and acetic anhydride (30 c.c.) were stirred together at 0° and kept in the ice-chest, with occasional stirring, for 7 days. Water was added, and the mixture left overnight in the ice-chest. Next day the product was filtered off and washed with water and with ether. It was ground with successive lots of a mixture of equal volumes of acetone and ether (10 c.c. × 16) until the filtrates were blue. The undissolved residue amounted to a 30% yield (0·59 g.)

(Found: I, 21·6. $C_{29}H_{23}N_3IS_2$ requires I, 21·5%). The dull green crystals had m. p. 183° (decomp.). The methyl-alcoholic solution had a well-defined absorption band with maximum at 6400 A.

An attempt to prepare this dicarbocyanine by using sodium dissolved in alcohol as condensing agent was unsuccessful.

Trimethin[2-(3-*ethyldihydrobenzoxazole*)][2-(peri*naphtha*-1 : 3-*thiazine*)] (V).—2-Methyl*peri*naphtha-1 : 3-thiazine (3·98 g.; 1 mol.) and 2-β-acetanilidovinylbenzoxazole ethiodide (8·68 g.; 1 mol.) were fused together at 125° for 30 minutes. The reaction mixture was heated with sodium hydroxide solution, and the *base* extracted with chloroform. After removal of solvent, the residue was recrystallised from ethyl acetate (120 c.c.) and thus obtained in 38% yield (3·08 g.) (Found: S, 8·5. $C_{23}H_{18}ON_2S$ requires S, 8·7%). The dark red crystals had m. p. 165—168° (decomp.). Their pyridine or methyl-alcoholic solution had an absorption band which extended from 4000 to 4900 A., with maxima at 4300 and 4550 A. Addition of sulphuric acid to the latter (5 g. per 100 c.c.) resulted in an absorption curve with definite maxima at 4900 and 5200 A. The dye is a weak sensitiser, giving a broad band which extends past 6000 with an indefinite maximum at 5500 A.

Trimethin[2-(3-*ethyldihydrobenzoxazole*)][2-(peri*naphtha*-1 : 3-*thiazine*)] *Hydrochloride*.—A suspension of trimethin-[2-(3-ethyldihydrobenzoxazole)[2-(*peri*naphtha-1 : 3-thiazine)] (0·5 g.) in spirit (5 c.c.) was stirred and heated with concentrated hydrochloric acid (3 c.c.) and water (10 c.c.). The resultant *hydrochloride* (0·55 g.) was dissolved in absolute alcohol (5 c.c.) and by precipitation with ether was obtained in 85% yield (Found: Cl, 8·8. $C_{23}H_{19}ON_2SCl$ requires Cl, 8·7%). The bright red crystals had m. p. 200° (decomp.). Its methyl-alcoholic solution absorbed from 4200 to 5400 A.; a strong absorption band had its maximum at 4800 and an inflexion at 4400 A., whilst a weaker one had its maximum at 5200. The distribution of sensitising is very like that of the base but the base is the stronger sensitiser. The maximum of the hydrochloride lies at 5500 A. and the sensitivity extends past 6100 A.

Trimethin[2-(3-*ethyldihydro*-4 : 5-*benzbenzoxazole*)][2-(peri*naphtha*-1 : 3-*thiazine*)].—2-Methyl*peri*naphtha-1 : 3-thiazine and 2-β-acetanilidovinyl-4 : 5-benzbenzoxazole ethiodide were fused together at 140° for an hour, the product was heated with alkali, and the base extracted with chloroform. The crude *base* was purified by heating and stirring with caustic alkali and benzene, and it crystallised from the concentrated benzene extract in 24% yield (Found: S, 7·85. $C_{27}H_{20}ON_2S$ requires S, 7·65%). The bright red solid had m. p. 190° (decomp.). Its pyridine or methyl-alcoholic solution had a very broad absorption band, extending from 4000 to 5400 A., with its maximum at 4750 A. After addition of sulphuric acid to the latter (5 g. per 100 c.c.), the curve had maxima at 4800, 5050, and 5400 A. The dye is a weak sensitiser with its maximum action at 5650 A.; it causes considerable depression of blue sensitivity.

Trimethin [2-(3-*ethyldihydro*-6 : 7-*benzbenzoxazole*)][2-(peri*naphtha*-1 : 3-*thiazine*)].—The preparation was carried out as in the preceding instance, except that 2-β-acetanilidovinyl-6 : 7-benzbenzoxazole ethiodide was used and heating was for 30 minutes at 130°. Purification was by heating and stirring with caustic alkali and benzene. From the concentrated benzene extract the *base* was precipitated by ether in 20% yield (Found: S, 7·8. $C_{27}H_{20}ON_2S$ requires S, 7·6%). The dark red solid had m. p. 155° (decomp.), with shrinking from 135°. Its pyridine or methyl-alcoholic solution absorbed from the ultra-violet up to about 5400, with a maximum at 4700 A. After addition of sulphuric acid to the latter solution (5 g. per 100 c.c.), the maximum was at 5400 A. with a secondary one at 5050 A. It is a weak sensitiser with maximum at 5700 A.; it depresses blue sensitivity a little.

Trimethin[2-(3-*ethyldihydrobenzthiazole*)][2-(peri*naphtha*-1 : 3-*thiazine*)] (VI).—2-Methyl*peri*naphtha-1 : 3-thiazine (1·99 g.) and 2-β-acetanilidovinylbenzthiazole ethiodide were fused together at 130—140° for an hour and the product was stirred on the steam-bath with 40% sodium hydroxide solution (15 c.c.) for 5 minutes. The base was extracted with chloroform and, after removal of the solvent, the residue was stirred on the steam-bath for 30 minutes with benzene (50 c.c.) and 20% sodium hydroxide solution (50 c.c.). The benzene solution was separated, washed with water, and concentrated; by addition of spirit the dye *base* was precipitated in 54% yield (Found: S, 16·5. $C_{23}H_{18}N_2S_2$ requires S, 16·6%). The dull red solid had m. p. 196° (decomp.). In methyl alcohol or pyridine solution, the dye had a broad absorption band, extending from the ultra-violet up to 5500 A. with its maximum at about 4600. On addition of sulphuric acid to the methyl-alcoholic solution (5 g. per 100 c.c.), the band became much narrower, with its maximum at 5550 A. It sensitised a gelatino-bromide photographic emulsion very weakly from 5500 to 6100 A. with the maximum effect at 5850.

Trimethin[2-(3-*ethyldihydro*-4 : 5-*benzbenzthiazole*)][2-(peri*naphtha*-1 : 3-*thiazine*)].—2-Methyl*peri*naphtha-1 : 3-thiazine and 2-β-acetanilidovinyl-4 : 5-benzbenzthiazole ethiodide were fused together at 140° for 1 hour. The product was heated with alkali and extracted with chloroform and the resultant *base* was purified by boiling and stirring for 30 minutes with benzene and 20% sodium hydroxide solution. The benzene layer was washed with water and concentrated, and dark red crystals separated in 36% yield (0·79 g.) (Found: S, 14·7. $C_{27}H_{20}N_2S_2$ requires S, 14·7%). M. p. 215° (decomp.). A pyridine or methyl-alcoholic solution showed a broad absorption band, extending from 4300 to 5700 A. On addition of sulphuric acid to the latter (5 g. per 100 c.c.), the absorption band became narrower and moved towards the red, two practically equal maxima being discernible, at 5350 and 5750 A. It was a weak sensitiser, causing much depression of blue sensitivity; sensitising was practically uniform from 5000 to 6100, extending to 6700 A.

Trimethin [2-(3-*ethyldihydro*-6 : 7-*benzbenzthiazole*)][2-(peri*naphtha*-1 : 3-*thiazine*)].—The preparation was effected as in the previous case, but with use of 2-β-acetanilidovinyl-6 : 7-benzbenzthiazole ethiodide, and fusion was at 150°. After the product had been heated with alkali and benzene, the benzene extract was concentrated to small volume, and the *base* precipitated with ether. It was obtained in 35% yield (Found: S, 14·6. $C_{27}H_{20}N_2S_2$ requires S, 14·7%). The dark red solid had m. p. 212° (decomp.) with shrinking from 190°. Its pyridine or methyl-alcoholic solution showed a very broad absorption band from 4400—5500 A., with maxima at 4800 and 5200 A. On addition of sulphuric acid to the latter (5 g. per 100 c.c.), the absorption band moved towards the red and showed well-defined maxima at 5350 and 5700 A. The dye is a weak sensitiser to about 6400 with the maximum effect at 6150 A.; it depresses blue sensitivity.

Trimethin [2-(3-*ethyldihydro*-6 : 7-*benzbenzthiazole*)][2-(peri*naphtha*-1 : 3-*thiazine*)] *Hydrochloride*.—A suspension of trimethin [2-(3-ethyldihydro-6 : 7-benzbenzthiazole)][2-(*peri*naphtha-1 : 3-thiazine)] (0·5 g.) in spirit (5 c.c.) was heated, concentrated hydrochloric acid (3 c.c.) and water (10 c.c.) added, and the mixture boiled for 3 minutes. The solution was cooled, and the crystals filtered off and washed with water and benzene. After recrystallisation from methyl alcohol (300 c.c. per g.), the yield was 59% (Found: Cl, 7·3. $C_{27}H_{21}N_2S_2Cl$ requires Cl, 7·5%). The dark product had m. p. 218° (decomp.). In methyl-alcoholic solution it seemed to dissociate, since the broad absorption band was like that of the parent base, but on acidification of the solution with hydrochloric acid the band moved towards the red and became narrower, showing a well-defined maximum at 5750 A. and a weaker one at 5250 A. The distribution of sensitising was similar to that of the base, but it gave weaker sensitising and less depression of blue sensitivity than did the base.

[2-(3-*Ethylbenzoxazole*)][2-(3-*methyl*peri*naphtha*-1 : 3-*thiazine*)]*trimethincyanine Iodide* (VII; R = Me).—Trimethin-[2-(3-ethyldihydrobenzoxazole)][2-(*peri*naphtha-1 : 3-thiazine)] (V) (0·74 g.; 1 mol.) was heated with methyl iodide (0·25 c.c.; 2 mols.) in a sealed tube at 100° for 2 days. The resultant *methiodide* was boiled out with benzene (15 c.c.) and washed with ether. After recrystallisation from methyl alcohol (30 c.c.), it was obtained in 39% yield (0·4 g.) (Found: I, 24·65. $C_{24}H_{21}ON_2IS$ requires I, 24·8%). The dark red substance had m. p. 202° (decomp.). Its absorption maximum is at 5150 A. It is a very weak sensitiser, with maximum at 5500 A., and causes considerable depression of blue sensitivity.

[2-(3-*Ethylbenzoxazole*)][2-(3-*ethyl*per*inaphtha*-1 : 3-*thiazine*)]*trimethincyanine Iodide* (VII; R = Et).—Trimethin-[2-(3-ethyldihydrobenzoxazole)][2-(*peri*naphtha-1 : 3-thiazine)] (1 g.) was heated with ethyl iodide in a sealed tube at 100° for 2 days. After boiling out with benzene and grinding with ether, the *ethiodide* (1·16 g.) was recrystallised from methyl alcohol (30 c.c.) and obtained in 46% yield (0·65 g.) (Found: I, 24·1. $C_{25}H_{23}ON_2IS$ requires I, 24·1%). The dark crystalline substance had m. p. 173° (decomp.). The absorption maximum is at 5100 A., with a secondary maximum at 4850. It is a weak sensitiser, with maximum at 5500 A., and depresses the blue sensitivity.

2-p-*Dimethylaminostyryl*per*inaphtha*-1 : 3-*thiazine Methomethylsulphate* (VIII; R = Me, X = SO_4Me).—2-Methyl-*peri*naphtha-1 : 3-thiazine methomethylsulphate (3·25 g.; 1 mol.), *p*-dimethylaminobenzaldehyde (1·49 g.; 1 mol.), and absolute ethyl alcohol (40 c.c.) were boiled together for 15 minutes. The product (2·4 g.; 53% yield) was purified by grinding first with ether and then with acetone, after which the yield was 48% (Found: S, 14·2. $C_{23}H_{24}O_4N_2S_2$ requires S, 14·05%). The dark solid had m. p. 116° (decomp.). The absorption maximum of a methyl-alcoholic solution is at 5520 A. The dye gave practically no sensitising and depressed the blue speed of the plate. Joy and Bogert (*J. Org. Chem.*, 1936, **1**, 236) give 4700 A. as the absorption maximum of the methiodide.

2-p-*Dimethylaminostyryl*per*inaphtha*-1 : 3-*thiazine Hydriodide* (VIII; R = H, X = I).—2-Methyl*peri*naphtha-1 : 3-thiazine hydriodide (2 g.; 1 mol.), *p*-dimethylaminobenzaldehyde (1 g.; 1·1 mols.) and absolute ethyl alcohol (25 c.c.) were boiled together for 5 minutes. The crude solid was purified by grinding with ether and resulted in 38% yield (1·09 g.) (Found: I, 27·9. Calc. for $C_{21}H_{19}N_2IS$: I, 27·7%). M. p. 235—240° (decomp.). The absorption maximum of a methyl-alcoholic solution, acidified with hydrochloric acid to prevent dissociation, is at 5430 with a weaker one at 5100 A. Joy and Bogert give the absorption maximum as 4500 A. (*loc. cit.*).

2-p-*Dimethylaminostyryl*per*inaphtha*-1 : 3-*thiazine* (IX).—2-Methyl*peri*naphtha-1 : 3-thiazine (1·99 g.; 1 mol.), *p*-dimethylaminobenzaldehyde (1·49 g.; 1 mol.), and concentrated hydrochloric acid (15 c.c.; 1·1 mols.) were heated together on the steam-bath for 30 minutes. The solid product was taken up in hot methylated spirit, and the filtered solution treated with excess of ammonia. The base was filtered off, washed (2·97 g. obtained), and crystallised from benzene (90 c.c.). The yield of orange crystals was 59% (Found: S, 9·8. $C_{21}H_{18}N_2S$ requires S, 9·7%). M. p. 213° (decomp.). The absorption maximum of a methyl-alcoholic solution was at 4170 A., and on addition of sulphuric acid (5 g. per 100 c.c.) moved to 5430 A.

We are indebted to Dr. B. H. Carroll and Dr. E. P. Davey for testing the sensitising action of the compounds and to Miss M. D. Gauntlett and Mr. E. D. Rowell for photographing the absorption spectra.

KODAK LTD., WEALDSTONE, HARROW, MIDDLESEX. [*Received, July 19th*, 1943.]

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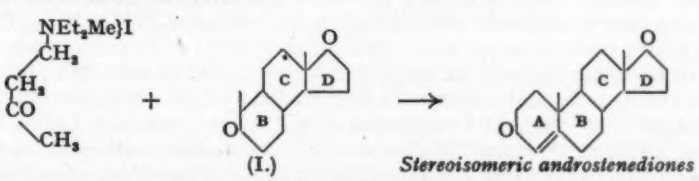
132. *Experiments on the Synthesis of Substances related to the Sterols. Part XLI. Androstenedione. Part I.*

By R. H. MARTIN and SIR ROBERT ROBINSON.

Theory predicts the existence of sixteen optically inactive (*dl*) stereoisomerides of androstenedione, but these are divided into two groups of eight when the relative configuration of two asymmetric centres is fixed. The present communication describes a method by means of which it is believed that such a mixture of a maximum of eight *dl*-stereoisomerides (probably fewer) has been obtained.

We are here concerned only with the elaboration of the androstenedione structure and the substance itself is most probably included in the second group of stereoisomerides, in which series the penultimate stage has been reached. If our interpretation of the final reaction in the synthesis (see below) proves to be incorrect, the method can nevertheless be used, with a small modification of procedure and one additional stage.

IN Part XXX (Robinson and Weygand, J., 1941, 386) a synthesis of testosterone was foreshadowed by the condensation of a keto-alcohol [the *cyclo*pentanol corresponding to (I)] with 4-diethylaminobutan-2-one methiodide in the presence of basic catalysts. This followed the proof that a similar condensation with 1-methyl-2-decalone afforded a phenanthrene derivative including the testosterone structure of rings A and B. Earlier work (du Feu, McQuillin, and Robinson, J., 1937, 53; cf. Rapson and Robinson, J., 1935, 1285) had shown that this type of condensation always involved a group $-CHMe\cdot CO-$ in preference to $-CH_2\cdot CO-$. This conclusion, based on several proved cases, is not invalidated with the particular component mentioned by the observation that acetyl*cyclo*hexene in an analogous process attacks the keto-methylene group (Jones and Koch, J., 1942, 393 and private communication; cf. Rapson and Robinson, *loc. cit.*); the steric conditions are quite different in this example. For these reasons we decided, in the first instance, to attempt the synthesis of androstenedione by way of the diketone (I) in the hope that neither keto-methylene group would enter into reaction and that the process would take the course illustrated below.

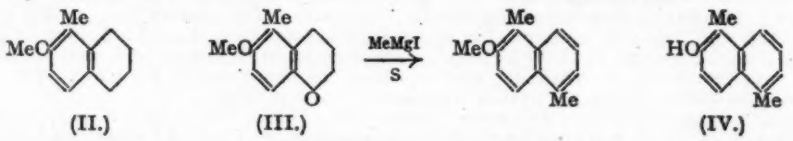


We have realised this scheme but have not yet proved the validity of the assumption made in regard to the constitution of the products.

The synthesis of (I) has been carried out by adaptations of methods adumbrated in this series of papers (*e.g.*, Robinson and Schlittler, J., 1935, 1288; Robinson and Walker, J., 1936, 747; 1937, 1160; 1938, 183; Litvan and Robinson, J., 1938, 1997) and which with small, but useful, modifications of detail have been

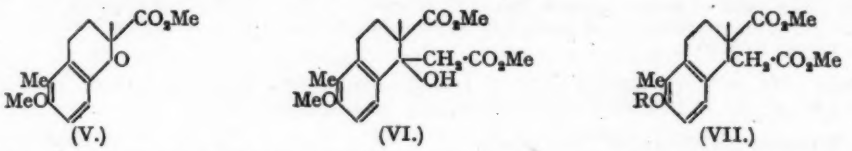
employed by Bachmann and his collaborators in the synthesis of equilenin and some analogous substances (Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1939, **61**, 974; 1940, **62**, 824; and other papers).

The starting point in the present work was 1-methyl-2-naphthol, which was catalytically reduced and methylated to *6-methoxy-5-methyltetralin* (II). On oxidation with chromic acid this substance afforded 6-methoxy-5-methyl-1-tetralone (III),* the constitution of which was proved by its conversion into 1 : 5-dimethyl-2-naphthol (IV) (Ruzicka and Sternbach, *Helv. Chim. Acta*, 1940, **23**, 355).



(II.) (III.) (IV.)

A further proof of the constitution of (III) is afforded by its conversion into 2 : 5-dimethoxy-1-methylnaphthalene (Cornforth, Cornforth, and Robinson, J., 1942, 690). This substance can also be obtained from 1 : 6-dihydroxynaphthalene by a series of processes (the work forms part of a separate investigation and will be published later). A third link with known substances is mentioned in the experimental section. Condensation of (III) with methyl oxalate, heating of the product with loss of carbon monoxide, and *C*-methylation of the resulting β-ketonic ester afforded (V). The Reformatzky reaction with methyl bromoacetate then gave (VI).

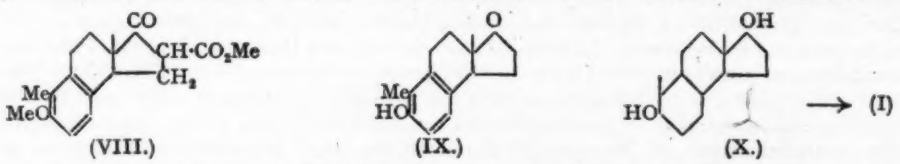


(V.) (VI.) (VII.)

This ester was dehydrated and reduced to stereoisomeric forms of (VII, R = Me), the details of the methods of Bachmann *et al.* (*loc. cit.*; also Bachmann and Thomas, *J. Amer. Chem. Soc.*, 1941, **63**, 598) being followed at these stages. We obtained an *α-dimethyl* ester, m. p. 112—113°, and a more readily soluble β-*dimethyl* ester, m. p. 53—54°. The corresponding α- and β-*dicarboxylic acids* give their respective *anhydrides* without configurational change. It appeared possible that a determination of spatial structure could be made by comparison of the first and the second dissociation constants of these acids (cf. Speakman, J., 1941, 940), but Dr. Speakman, who very kindly made the necessary measurements, reports that the observed differences are not significant in this case. On grounds of analogy we are of the opinion that the more readily soluble β-series correspond in configuration to the natural hormones, and this was the experience of Bachmann and his colleagues in connexion with the intermediates from equilenin. This implies that CO_2Me and $CH_2{\cdot}CO_2Me$ are in the *cis*-position in the α-series and *trans*- in the β-series.

The α-derivatives were, however, obtained in the larger relative amount and accordingly the later stages were first examined in this series.

Conversion of (VII) (α) into (VIII) (α) was accomplished by the application of the Arndt-Eistert homologation process as developed by Litvan and Robinson (*loc. cit.*) for the transformation of *O*-methylœstric acid into œstrone. At the last stage the *cyclo*pentanone ring was closed by the Dieckmann reaction (cf. Bachmann *et al.*, *loc. cit.*). The keto-ester was hydrolysed and demethylated in one operation to the phenolic ketone (IX).



(VIII.) (IX.) (X.)

Subsequently these reactions were carried out in the β-series also and the β-tricyclic phenolic *ketone* (IX) was isolated.

In order to proceed further it was necessary to reduce the aromatic nucleus at some stage and our first experiments in this direction were made with the phenolic α-di-ester (VII; R = H). This substance was either not reduced in useful yield or under more vigorous conditions of hydrogenation suffered loss of oxygen by hydrogenolysis. In these experiments we employed Raney nickel at 180—200°/150 atms. The failure led us to investigate other catalysts for high-pressure hydrogenation and the results are of general interest. Adkins (" Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," Wisconsin Univ. Press, 1937, p. 7) writes: " One would conclude that with platinum, for example, there is already a sufficient proportion of hydrogen upon the catalyst at one or two atmospheres pressure, since in general an increase of pressure of hydrogen does not increase the rate of hydrogenation."

There are few references to the use of platinum or palladium at higher temperatures and pressures. Spongy palladium has been used by Breteau (*Bull. Soc. chim.*, 1911, **9**, 729) for the vapour phase reduction of

* We find that this ketone, m. p. 114—115° (corr.), has previously been prepared by a nuclear synthetic method by Ruzicka and Hofmann (*Helv. Chim. Acta*, 1937, **20**, 1155).

phenanthrene at 150—160°. We have found, however, that 2% palladised strontium carbonate is an excellent catalyst for pressure hydrogenations at elevated temperatures. It does not appear to have been previously employed for this purpose. (*a*) Phenol was quantitatively hydrogenated to *cyclo*hexanol in dioxan at 140—150°/123 atms. (*b*) Quinol dimethyl ether is reduced in dioxan to 1 : 4-dimethoxy*cyclo*hexane at 200°/100 atms. According to Adkins (*op. cit.*, p. 59) this substance is not reduced in presence of Raney nickel at 225°/100—200 atms. but can be hydrogenated at 200° with the help of reduced nickel on kieselguhr. (*c*) Ethyl *p*-hydroxybenzoate was quantitatively reduced to *trans*-4-carbethoxy*cyclo*hexanol in dioxan at 150—180°/150 atms. Here Raney nickel at 200°/160 atms. gave poor results and the present method of preparation of this important intermediate (and the related ketone) is greatly to be preferred to any of those already reported (Edson, *J. Soc. Chem. Ind.*, 1934, **53**, 138; Balas and Srol, *Coll. Trav. chim. Tchecoslovaquie*, 1929, **1**, 658; Mitsui, *Mem. Coll. Sci. Kyoto Imp. Univ.*, 1935, **18***A*, 329; cf. Perkin, J., 1904, **85**, 416).

Although we were unsuccessful in applying this method to (VII; R = H), it was found that the tricyclic phenol (IX) could be reduced to the dihydric alcohol (X). In later work it was noted that the purity of the dioxan employed as solvent was of the utmost importance. The product was a glass and 32 inactive stereoisomerides are theoretically possible (32 more in the β-series). Oxidation with chromic acid gave the diketone (I), which should exist in eight inactive stereoisomeric forms (α-series). Owing, however, to possible isomerisation of the group ·CO·CHMe· it is probable that four of these are labile forms and there are really four pairs of interconvertible diketones. A crystalline substance could be isolated in considerable relative amount from the mixture and there is little doubt that this particular isomeride preponderated.

The mixed diketones (I, α-series) were condensed with 4-diethylaminobutan-2-one methiodide after treatment with sodamide under the usual conditions, and mixed *ketones*, $C_{19}H_{26}O_2$, isolated. The absorption of an alcoholic solution confirmed the presence of an αβ-unsaturated ketonic group.

Biological tests have been made so far only with the tricyclic compounds of the α-series. The results were negative and will be published along with other similar data.

The α-tricyclic phenolic ketone (IX) is not œstrogenic (up to 5 mg.).

Experimental.

Throughout this investigation it has been found essential to pay particular attention to the purity of the reagents employed. Except in the case of dioxan, no further reference to this matter is made.

6-*Methoxy-5-methyltetralin* (II).—(*a*) The preparation of 2-methoxy-1-naphthaldehyde by the Tiemann–Reimer reaction with β-naphthol, followed by methylation (Fosse, *Bull. Soc. chim.*, 1901, **25**, 373), gave very unsatisfactory results.

The method of " Organic Syntheses " (XX, p. 11) for 2-ethoxy-1-naphthaldehyde gave a 67% yield when used for the methoxy-compound. Material of b. p. 153—154°/0·6 mm., m. p. 76—79° (81°, pure), (200 g.) was hydrogenated in ethyl alcohol (600 c.c.) at 100°/100 atms. for 3 hours in the presence of Raney nickel (20 g.). The product was crystallised in contact with chilled methanol (yield, 105 g.); recrystallised several times from methanol and sublimed at 50°/0·01 mm., it formed colourless plates, m. p. 51·5—52° (Found : C, 81·4; H, 9·0. $C_{12}H_{16}O$ requires C, 81·8; H, 9·2%). On demethylation with hot hydriodic acid and acetic acid it afforded 6-*hydroxy-5-methyltetralin*, snow-white silky needles, m. p. 113·5—114·5°, from light petroleum (b. p. 60—80°) (Found : C, 81·5; H, 8·9. $C_{11}H_{14}O$ requires C, 81·5; H, 8·8%).

(*b*) In the preparation of 1-methyl-2-naphthol (Cornforth, Cornforth, and Robinson, J., 1942, 682) the quantity of sodium methoxide can be reduced. We used methylenedinaphthol (150 g.), methanol (600 c.c.), and sodium (48 g.) and heated the mixture for 7 hours at 210°. The product was treated for ½ hour with formalin (50 c.c. of 40%), isolated, and distilled, b. p. 180—184°/23 mm. (average yield, 100 g.; best yield, 108 g.). This material (280 g.) was reduced in alcohol (500 c.c.) for 2—3 hours at 110°/100 atms. in the presence of Raney nickel (25 g.). The residue after evaporation was dissolved in aqueous sodium hydroxide (1000 c.c. of 20%), the hot solution diluted with water (8—10 l.), treated with charcoal, and filtered, and the phenol set free and collected. After purification of a small sample it had m. p. 113·5—114·5°, undepressed by admixture with the above analysed specimen of 6-hydroxy-5-methyltetralin. It was at once methylated by shaking a solution in water (1500 c.c.) and sodium hydroxide (200 g.) with methyl sulphate (300 c.c.) at 80°, with final heating on the steam-bath for 1½ hours. The neutral solid was collected, and phenolic material recovered from the alkaline solution and remethylated (30 c.c. of methyl sulphate). The combined product afforded 177 g. of distilled methoxymethyltetralone, as below, which is a 57% overall yield from methylnaphthol.

6-*Methoxy-5-methyl-1-tetralone* (III).—A solution of chromic anhydride (100 g.) in acetic acid (600 c.c.) and water (80 c.c.) was added dropwise to one of methoxymethyltetralin (100 g.) in acetic acid (1000 c.c.) with stirring and cooling to below 20°. After being stirred for 3 hours (ice-bath), the mixture was kept for 18 hours at room temperature. Methanol (50 c.c.) was added and after ½ hour the solvent was distilled under diminished pressure until frothing occurred. The residue was mixed with water (1·5 l.), and the solid collected and distilled, b. p. 185—195°/15 mm. (average yield, 70%). The crude, light yellow ketone, m. p. 103—105°, was crystallised from methanol, sublimed at 110°/0·1 mm., and recrystallised from methanol, being obtained in white plates, m. p. 112—113° (Found : C, 75·7; H, 7·3. Calc. for $C_{12}H_{14}O_2$: C, 75·8; H, 7·4%).

The 2 : 4-*dinitrophenylhydrazone* crystallised from xylene in dark red leaflets, m. p. 249—250° (Found : C, 58·6; H, 4·8; N, 15·2. $C_{18}H_{18}O_5N_4$ requires C, 58·4; H, 4·8; N, 15·2%). Conversion into the known 1 : 5-dimethyl-2-naphthol was effected as follows.

A solution of the ketone (2·5 g.) in ether (40 c.c.) and benzene (10 c.c.) was gradually added to one of methylmagnesium iodide (from 4·7 g. of magnesium) with ice-cooling. After 1 hour the product was isolated and found to be unsaturated to bromine and permanganate. It was dehydrogenated by means of sulphur (0·45 g.) at 215°, and the product distilled (1·8 g. of solid), crystallised from methanol, sublimed at 65°/0·1 mm., and recrystallised from methanol. 2-*Methoxy*-1 : 5-*dimethylnaphthalene* was obtained in white plates, m. p. 96—97° (Found : C, 84·1; H, 7·7. $C_{13}H_{14}O$ requires C, 83·8; H, 7·6%). On demethylation with hot hydriodic acid (*d* 1·7) and acetic acid the naphthol was produced; purified by sublimation at 150°/15 mm., it had m. p. 161—162° (Found : C, 84·0; H, 6·7. Calc. for $C_{12}H_{12}O$: C, 83·7; H, 6·9%) [Ruzicka and Sternbach, *loc. cit.*, give m. p. 162—163° (corr.)]. The benzoate, crystallised from methanol, had m. p. 149—150° [R. and S. give m. p. 151—151·5° (corr.)]. The m. p.'s cited in this communication are uncorrected.

Methyl 6-*Methoxy-5-methyl-1-tetralone-2-glyoxylate*.—A mixture of methyl oxalate (90·5 g.), dry powdered sodium

methoxide (from 17·7 g. of sodium), and benzene (570 c.c.) was refluxed under nitrogen for 20 minutes. It was then cooled and stirred during the addition (10 minutes) of methoxymethyltetralone (72 g.) in benzene (250 c.c.). The suspension was stirred for 1 hour at room temperature and for 4 hours on the steam-bath. After 12 hours, water was added, and the aqueous solution, together with further extracts by aqueous sodium hydroxide, acidified with hydrochloric acid. The precipitated product was collected, washed, and dried (yield, 93—94%). The *glyoxylate* crystallised from methanol in yellow needles, m. p. 136—137° (Found: C, 65·4; H, 5·8. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%). The ferric reaction in alcoholic solution was intense brown and the solution in sulphuric acid had a bright orange colour.

Methyl 6-Methoxy-5-methyl-1-tetralone-2-carboxylate.—A mixture of the above ester (76·7 g., crude) and powdered glass (30 g.) was heated at 170—180° until evolution of carbon monoxide ceased (½—¾ hour). The product was collected by means of benzene; it had b. p. 180—184°/0·4 mm., almost all at 182° (yield, 87%). The viscous oil slowly solidified; it was crystallised from methanol and from benzene–light petroleum, sublimed at 85°/0·0025 mm., and finally crystallised from benzene–light petroleum (b. p. 60—80°), forming thick, colourless prisms, m. p. 100—101° when immersed at 93° (Found: C, 68·0; H, 6·7. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%). The ferric reaction in alcoholic solution was dark green.

The 2 : 4-*dinitrophenylhydrazone* crystallised from benzene in feathery, brick-red needles, m. p. 223—224° after darkening at 195° (Found: C, 56·1; H, 4·8. $C_{20}H_{20}O_7N_4$ requires C, 56·1; H, 4·7%).

Methyl 6-Methoxy-2 : 5-dimethyl-1-tetralone-2-carboxylate (V).—A mixture of the above keto-ester (55 g.), benzene (250 c.c.), and methanol (250 c.c.) was added to a solution of sodium (25 g.) in methanol (500 c.c.) with stirring under nitrogen. After heating and cooling, methyl iodide (75 c.c.) was added and after 2 hours the mixture was refluxed for 8 hours and kept for 12 hours. The solution was just acidified with acetic acid, and most of the solvent distilled under diminished pressure. On addition of water and shaking, the precipitated oil solidified. It was collected, washed, dried, and distilled (b. p. 162—163°/0·4 mm.). It was found preferable to take the whole distillate and crystallise it from benzene–light petroleum (b. p. 60—80°) (80—85% yield, m. p. 84—86°, and about 89% on a smaller scale). The substance, recrystallised from the same solvent and sublimed at 90°/0·01 mm., formed transparent hexagonal prisms, m. p. 89—90·5° (Found: C, 68·5; H, 6·9. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). The ferric reaction was negative.

Methyl 1-Hydroxy-6-methoxy-2-carbomethoxy-2 : 5-dimethyltetralin-1-acetate (VI).—A mixture of methyl methoxydimethyltetralonecarboxylate (20 g.), benzene (160 c.c.), ether (160 c.c.), zinc filings (40 g.), methyl bromoacetate (15 c.c.), and iodine (0·5 g.) was heated at 70°. Reaction usually commenced within 15 minutes but sometimes only after some hours' refluxing. When brisk reaction occurred, further additions were made as follows: 1 hour, zinc (15 g.) and a crystal of iodine; 2 hours, zinc (15 g.), methyl bromoacetate (10 c.c.) and a crystal of iodine; 3 hours, zinc (15 g.) and a crystal of iodine; 4 hours, the same; 5 hours, the same with methyl bromoacetate (5 c.c.); 6 hours, the same, no ester. Vigorous stirring was maintained during this process and during the following 5 hours (bath kept at 70°). After 12 hours the complex was decomposed with water and acetic acid, and the zinc washed with ether. The organic layer was washed with aqueous ammonia and dried, and the solvents removed. The residue crystallised in contact with light petroleum (b. p. 60—80°) and was a bright yellow solid (yield, 80—85%). For analysis the substance was crystallised from benzene–light petroleum, adsorbed on alumina, eluted by chloroform (ether–benzene, 1 : 1, or ether was an ineffective solvent for this purpose), and finally recrystallised from benzene–light petroleum. It formed colourless prisms, m. p. 106·5—108° (Found: C, 64·3; H, 7·1. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·2%). When pure benzene was employed as solvent in the reaction, the yield was much lower.

Derivatives of 1-Carboxymethylene-6-methoxy-2 : 5-dimethyltetralin-2-carboxylic Acid.—Anhydride. A solution of the Reformatzky product (12·5 g.) in benzene (35 c.c.) was gradually added to a mixture of thionyl chloride (11 c.c.), pyridine (5·5 c.c.), and benzene (50 c.c.) cooled in ice-salt. After ¾ hour at room temperature, with frequent shaking, ice-water was added and the benzene layer, mixed with potassium hydroxide (13 g.) and methanol (200 c.c.), was refluxed for ½ hour. Aqueous potassium hydroxide (40 c.c. of 40%) was then added, and refluxing continued for ¾ hour. Water was introduced, and the solution distilled until it was homogeneous; it was then refluxed for 4 hours. Most of the alkali was neutralised, and insoluble material (1·1 g.) separated. The filtrate was acidified, and the precipitate collected (8·4 g.; on a larger scale 64 g. gave 49·5 g.). This material (A) is a mixture of *cis*-anhydride and *trans*-dicarboxylic acid. On crystallisation from acetic acid, the *anhydride* was obtained in transparent, colourless prisms, m. p. 204—205° (Found: C, 70·7; H, 6·1. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). In one experiment 6-*methoxy*-2 : 5-*dimethyl*-1-*tetralone* was isolated as a non-saponifiable by-product. It crystallised from methanol in white prisms, m. p. 113—114° (Found: C, 76·8; H, 8·0. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·9%). The 2 : 4-*dinitrophenylhydrazone* crystallised from benzene–alcohol in dark red prisms, m. p. 229° (Found: N, 14·3. $C_{19}H_{20}O_5N_4$ requires N, 14·6%).

When the Reformatzky product was treated with sulphuric acid in benzene at room temperature and then at 50°, the above anhydride, m. p. 205—206°, was one of the products, but the process is not recommended as a method of preparation.

Dimethyl ester. A mixture of the above Reformatzky product (13·3 g.), calcium chloride (4 g.), and benzene (100 c.c.) was saturated with hydrogen chloride at room temperature and kept for 12 hours. It was then washed with aqueous sodium carbonate, dried, and passed through an alumina column, which removed colouring matters (a dark brown upper band and then a bright yellow band). The benzene solution was evaporated; the residue (B) partly crystallised in contact with methanol. The solid (6·3 g.), recrystallised from methanol, formed colourless needles, m. p. 105·5—106·5° (Found: C, 68·0; H, 6·8. $C_{18}H_{22}O_5$ requires C, 67·9; H, 7·0%). The pale yellow oil in the mother liquor was unsaturated; b. p. 150°/0·05 mm. (Found: C, 68·0; H, 6·9%). The disposition of the ω-carbomethoxyl group is evidently the cause of stereoisomerism in this case.

α- and β-Forms of 2-Carboxy-6-methoxy-2 : 5-dimethyltetralin-1-acetic Acid and Derivatives (as VII, R = Me).—(1) The crude anhydride (A, above) (5·6 g.) was hydrolysed with the minimum quantity of alcoholic potassium hydroxide and after evaporation of the solvent the resulting potassium salts were dissolved in water (120 c.c.) and reduced with sodium amalgam (150 g. of 2%). The dihydro-acids were isolated in the usual way and esterified in cold ethereal solution by means of diazomethane. The product was crystallised from a little methanol (refrigerator) and after 12 hours, 2·8 g., m. p. 108—110°, were collected. This α-*dimethyl* ester (VII, R = Me) crystallised from methanol in transparent, colourless plates, m. p. 112—113° (Found: C, 67·2; H, 7·5. $C_{18}H_{24}O_5$ requires C, 67·5; H, 7·6%). The β-*dimethyl* ester (VII, R = Me) in the mother-liquor would not crystallise, but on semi-hydrolysis it afforded a crystalline half-ester (see below). This was esterified with diazomethane and the product was again a somewhat intractable oil. It eventually crystallised from light petroleum (b. p. 60—80°) containing a little acetone. The derivative then crystallised from light petroleum in transparent, colourless prisms, m. p. 53—54° (Found: C, 67·5; H, 7·6%).

(2) The catalytic reduction of the unsaturated dimethyl ester (B, above) has been studied under different conditions and we give the yield of the solid α-dimethyl ester obtained. The oily material in the mother-liquors is doubtless largely the β-dimethyl ester, but it may still contain some α-ester and possibly other impurities. (*a*) With Adams's catalyst (25 mg.) in acetic acid (30 c.c.) at room temperature; 4 g. gave 3·4 g., m. p. 108—110°. (*b*) Similarly in ethyl acetate; reduction was slower and 2·5 g. gave 2·2 g. of α-ester. (*c*) Similarly in methanol or dioxan; reduction did not occur. (*d*) Palladium-black in acetone under similar conditions; rapid reduction, 2·5 g. gave 2·2 g. of the α-ester. (*e*) Similarly

with palladised charcoal; 10·5 g. gave 8·6 g. of α-ester. (*f*) Palladised strontium carbonate (2%); 2·6 g. gave 2·0 g. of α-ester. (*g*) Raney nickel at 60°/25 atms.; 4 g. gave 2·65 g. of α-ester [see (5)].

(3) The α- and *β-dicarboxylic acids* were obtained from the respective dimethyl esters. The α-ester (4 g.) was refluxed for 3 hours with aqueous potassium hydroxide (30 c.c. of 40%) and methanol (30 c.c.). The potassium salt that separated on cooling (long, silky, white needles) was collected, washed with methanol, dissolved in water, and acidified with hydrochloric acid. The gummy precipitate slowly crystallised and was converted, by refluxing for 2 hours with acetic anhydride, into the *α-anhydride*, which crystallised from acetic acid in microscopic snow-white needles, m. p. 173—174° (Found: C, 70·0; H, 6·7. $C_{16}H_{18}O_4$ requires C, 69·9; H, 6·6%). After hydrolysis with alkali and recovery the *α-dicarboxylic acid* crystallised from ethyl acetate in white prisms, m. p. 217—217·5° after slight sintering (Found in material dried over phosphoric oxide in a high vacuum: C, 65·8; H, 7·0. $C_{16}H_{20}O_5$ requires C, 65·7; H, 6·9%).

The *β-anhydride*, made in the same way, except that the potassium salt of the acid did not crystallise, separated from acetic acid in transparent prisms, m. p. 168—169° (Found: C, 70·1; H, 6·7%). The *β-dicarboxylic acid* crystallised from a little chilled ethyl acetate in prisms, m. p. 198—200° (Found: C, 65·9; H, 7·1%).

We are very grateful to Dr. J. C. Speakman of Sheffield University for the following report on the thermodynamic dissociation constants of the α- and the β-dicarboxylic acid.

Experiments in aqueous solution. The acids, though not very soluble, were sufficiently so to allow measurements to be made in aqueous solution. The β-acid was the more soluble of the two, and solutions about M/2000 could be obtained. On heating, the α-acid gave solutions almost as concentrated; these were supersaturated at room temperature, and deposited crystals overnight.

Experimental method. 0·010—0·015 G. of the acid (sometimes finely ground) was weighed, transferred to a Pyrex beaker and heated (if necessary to boiling) to bring about dissolution. The solution was then cooled and made up to 100 c.c. 40 C.c. portions were potentiometrically titrated with approximately N/30-sodium hydroxide (free from carbonate), a glass electrode being used. Experiments on the two isomers were carried out consecutively, each in turn being dealt with first. The pH-scale was standardised by interspersing amongst the above titrations similar ones using adipic acid, to the pK_1 value of which the value 4·40 was attributed (cf. J., 1940, 855, where other details are also given). The temperature was 20·0°.

Experiments in aqueous acetone. Experiments were also carried out in dilute aqueous acetone, though the glass electrode does not behave quite so conveniently in such mixed solvents. More concentrated solutions could be made rather more easily. The procedure was to weigh out the acid, transfer it to a 100 c.c. flask with 8 c.c. of acetone (which had been distilled from potassium carbonate), dissolve by shaking, and make up to the mark with water. The solutions (especially those of the α-acid) were apt to deposit crystals on standing. They were titrated in the way described.

Results ($pK = -\log_{10}K$; $\Delta pK = \log_{10}K_1/K_2$):

		pK_1.	pK_2.	ΔpK.	No. of expts.
Aqueous solns.:	α-Acid	4·37	5·63	1·26	8
	β-Acid	4·42	5·70	1·28	8
Aqueous acetone solns.:	α-Acid	4·51	5·75	1·24	5
	β-Acid	4·52	5·78	1·26	3

The (average) pK values are probably accurate to ±0·05, the ΔpK's to ±0·03.

Discussion. Although the results are unfortunately equivocal so far as the allocation of configurations is concerned, they quite certainly show that the ΔpK values are much closer together here than they are with the corresponding *cyclo*pentane-1-carboxylic-2-acetic acids (*cis*, 1·39; *trans*, 1·28). They tend in fact towards the value for glutaric acid itself (1·11).

Two points may have some relevancy: (i) The *cyclo*pentane ring is presumably (but not quite certainly) coplanar: the six-membered ring in these dibasic acids will be puckered. Hence in the *cis*-isomer the two carboxyl groups will probably be able to avoid the close approach that occurs between the carboxyl groups in the *cis-cyclo*pentane diacid.

(ii) In the *trans*-acid the methyl group might conceivably exert what Hammett calls a "proximity effect" on the carboxyl group of the acetic acid residue. If this effect did obtain, it can easily be argued that it will tend to raise ΔpK for the *trans*-acid. A few preliminary measurements on *cis*-1-methyl*cyclo*hexane-1-carboxylic-2-acetic acid gave a ΔpK value of 1·34, which is perhaps significantly lower than that for the *cis-cyclo*pentane-1-carboxylic-2-acetic acid mentioned earlier.

(4) The experiences of Litvan and Robinson (*loc. cit.*) and Bachmann *et al.* (*loc. cit.*) as well as other analogies make it certain that the monomethyl esters, obtained by semi-hydrolysis of di-esters, are correctly represented by the formula $C_{13}H_{16}O(CO_2Me)\cdot CH_2\cdot CO_2H$. A mixture of the α-dimethyl ester (6·4 g.), methanol (100 c.c.), and 1·03N-sodium hydroxide (19·4 c.c.) was refluxed for 6 hours. Most of the methanol was distilled, and the solution filtered from a little unchanged material, acidified, and extracted with ether. The *product* slowly crystallised (C) from benzene–light petroleum (b. p. 40—60°) in the refrigerator; recrystallised in the same way, it formed colourless prisms, m. p. 137—139° (Found: C, 66·4; H, 7·2. $C_{17}H_{22}O_5$ requires C, 66·6; H, 7·3%).

The *β-monomethyl* ester, prepared in similar fashion, was crystallised from ethyl acetate, distilled at 0·01 mm. (bath at 160°), and recrystallised from ethyl acetate. It formed white prisms, m. p. 149—150° (Found: C, 66·7; H, 7·5%).

(5) The reduction in presence of Raney nickel as described under (2) (*g*) is unreliable and in one experiment a large part of the product was degraded. After hydrolysis with alcoholic potassium hydroxide, neutral, monobasic acidic and dibasic acidic fractions were separated. The acids were heated with acetic anhydride, after which the neutral anhydride of the unsaturated dicarboxylic acid, m. p. 204°, described above, was isolated.

The original neutral product was crystallised from methanol, sublimed at 70°/0·1 mm., and recrystallised from methanol. It formed white plates, m. p. 89—90° (Found: C, 83·8; H, 8·3. Calc. for $C_{14}H_{16}O$: C, 84·0; H, 8·1%). The unstable picrate crystallised from alcohol in dark brown needles, m. p. 127—128° (decomp.), and the brilliant red *s*-trinitrobenzene adduct crystallised from alcohol in needles, m. p. 146°. The substance is clearly 6-methoxy-1 : 2 : 5-trimethylnaphthalene, already synthesised by Ruzicka, Hofmann, and Schellenberg (*Helv. Chim. Acta*, 1936, **19**, 1391), who give m. p. 89—90° (corr.), trinitrobenzene compound, m. p. 146—147° (corr.). Incidentally this is a further proof of the correctness of the constitution assigned to the α-tetralone (III). The monobasic acidic fraction crystallised from methanol in long, white needles, m. p. 180—192° (Found: C, 73·3; H, 7·2. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). The substance is soluble in aqueous sodium carbonate and unsaturated; the unsharp m. p. was not altered by several recrystallisations and may be due to lactonisation. It gives a red coloration with alcoholic picric acid and appeared to form a complex with *s*-trinitrobenzene. Hence this acid is probably a dihydronaphthalene derivative and if it is formed without migration of a group it should be *6-methoxy-2 : 5-dimethyl-3 : 4-dihydronaphthalene-1-acetic acid.*

On hydrogenation of 0·9 g. in ethyl acetate–acetone (60 c.c., 1 : 1) in the presence of palladised strontium carbonate (2%) the theoretical volume of hydrogen was absorbed in 30 minutes at the ordinary temperature and pressure.

6-Methoxy-2 : 5-dimethyltetralin-1-acetic acid crystallised from alcohol in white prisms, m. p. 155·5—157° (Found : C, 72·6; H, 8·0. $C_{15}H_{20}O_3$ requires C, 72·5; H, 8·1%). It gave no coloration with alcoholic picric acid.

Derivatives of α- and β-2-carboxy-6-hydroxy-2 : 5-dimethyltetralin-1-acetic acid (as VII, R = H). The above α-dimethyl ester (2 g.) was demethylated and hydrolysed by refluxing for 3 hours with hydriodic acid (6 c.c. *d* 1·7) and acetic acid (15 c.c.). After addition of water (no precipitate) the solution was extracted ten times with ether, and the extract washed with aqueous sodium bisulphite, and saturated brine, and dried. After evaporation of the solvent, the residue (m. p. *ca.* 220°; probably hydroxy-dicarboxylic acid) was refluxed for 2 hours with methanol (50 c.c.) and sulphuric acid (1 c.c.). A little water was added, most of the methanol distilled, more water added, and the solution extracted seven times with ether. The extract was washed successively with brine, 10% aqueous sodium carbonate and 10% aqueous sodium hydroxide. The soda washings were acidified, thoroughly extracted with ether, the acid rendered to sodium bicarbonate solution and recovered as before. The product was crystallised from methanol; it melted at 100° and resolidified and was recrystallised from chloroform, being obtained in colourless, microscopic prisms, m. p. 169—170°, containing solvent of crystallisation (Found in material dried at 100° in a high vacuum : C, 65·9; H, 6·8. $C_{16}H_{20}O_5$ requires C, 65·7; H, 6·9%). This substance is formed by semi-esterification of the dicarboxylic acid and is therefore *methyl α-2-carboxy-6-hydroxy-2 : 5-dimethyltetralin-1-acetate*, $HO{\cdot}C_{12}H_{13}(CO_2H){\cdot}CH_2{\cdot}CO_2Me$. The washings with 10% aqueous sodium hydroxide doubtless contained initially the hydroxy-dimethyl ester but hydrolysis supervened. The product was recovered as above; it crystallised from aqueous methanol in clusters of colourless needles, m. p. 179·5—180·5° (large depression with the isomeride, m. p. 169—170°) (Found : C, 66·1; H, 7·1%). The substance is readily soluble in aqueous sodium carbonate and is regarded as *α-2-carbomethoxy-6-hydroxy-2 : 5-dimethyltetralin-1-acetic acid*, $HO{\cdot}C_{12}H_{13}(CO_2Me){\cdot}CH_2{\cdot}CO_2H$. When the crude product of the demethylation of the α-dimethyl ester (or the α-dicarboxylic acid) was refluxed for 4 hours with methanol (4 vols.) and sulphuric acid (1 vol.), the dimethyl ester (VII, R = H) of the phenolic dicarboxylic acid was produced. Its ethereal solution was washed with aqueous sodium bicarbonate and the residue, after evaporation, was crystallised from benzene–light petroleum, distilled at 160—180°/0·1 mm., and recrystallised from methanol, being obtained in colourless prisms, m. p. 122—123° (Found : C, 66·4; H, 7·4. $C_{17}H_{22}O_5$ requires C, 66·6; H, 7·3%).

The β-dicarboxylic acid of the preceding section was similarly demethylated, and the product esterified by means of methanolic hydrogen chloride for 1 hour under reflux. The isolated product, freed from acids, crystallised from aqueous methanol (charcoal) in white prisms, m. p. 125—126° (Found : C, 66·4; H, 7·2%). There was a large depression of m. p. on admixture with the isomeride, m. p. 122—123°. All the phenolic substances described in this section coupled readily with *p*-nitrobenzenediazonium salts to give red azo-compounds.

Methyl 2-Carbomethoxy-6-hydroxy-2 : 5-dimethyldecalin-2-acetate.—Experiments on the per-hydrogenation of substances described in the last two sections gave very unpromising results; only one example will be briefly described. The phenolic α-dimethyl ester, m. p. 122—123°, (3 g.) was hydrogenated in dry dioxan (100 c.c.) in the presence of Raney nickel (0·5 g.). Starting at 20°/119 atms., the conditions after 1 hour were 190°/155 atms., after 2 hours, 220°/172 atms. and after 4 hours, 214°/172 atms.; the autoclave was then allowed to cool. Extraction of the ethereal solution of the products with 10% sodium hydroxide solution afforded 0·9 g. of phenolic monomethyl ester, m. p. 178—180°, which was esterified to the dimethyl ester, m. p. 122—123°. The neutral moiety was a mobile oil, which was fractionated as follows : (*a*) bath at 175°/0·1 mm. (Found : C, 70·1; H, 9·9. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%); (*b*) bath at 180°/0·1 mm. (Found : C, 67·0; H, 9·2%); (*c*) bath at 180°/0·05 mm. (Found : C, 65·7; H, 8·8. $C_{17}H_{28}O_5$ requires C, 65·4; H, 9·0%). The fraction (*a*) is probably largely deoxygenated in position 6, and (*c*) appears to be the desired product. The yield was hopelessly inadequate and this was the best result obtained along these lines, which we were forced to abandon.

Methyl α-2-Carbomethoxy-6-methoxy-2 : 5-dimethyltetralin-1-β-propionate.—The α-monomethyl ester (C, above) (5·1 g.) was converted into the chloride by means of thionyl chloride in ethereal solution containing 2 drops of pyridine. After 1 hour at room temperature the mixture was evaporated at 40°, several small volumes of benzene added, and the evaporation repeated after each addition. A benzene solution (60 c.c.) of this derivative was added dropwise to an ethereal solution of diazomethane (from 15 g. of nitrosomethylurea). After ½ hour at room temperature, the solution was evaporated (below 30°) under diminished pressure. The residual diazo-ketone was dissolved in methanol (65 c.c.) and treated at 70° with freshly prepared methanol–moist silver oxide (from 12 c.c. of 10% silver nitrate solution) added in three portions within ½ hour. When the evolution of nitrogen ceased, the solution was passed through an alumina column and evaporated. The oily product was extracted with boiling light petroleum (150 c.c. of b. p. 40—60°) (charcoal), and the solution concentrated to 30—40 c.c. It deposited 3·6 g., m. p. 81—83°, on keeping at a low temperature. After two recrystallisations the colourless needles had m. p. 84—85° (Found : C, 68·4; H, 7·8. $C_{19}H_{26}O_5$ requires C, 68·2; H, 7·9%).

Methyl 3′-Keto-6-methoxy-2 : 5-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 2-cyclopentenonaphthalene-2′-carboxylate (α- and β-Forms) (VIII).—A mixture of the above homologated α-ester (2·1 g.), dry sodium methoxide (0·3 g. of sodium), and benzene (20 c.c.) was refluxed under nitrogen for 2 hours. The neutral product, isolated in the known manner, was crystallised from light petroleum (b. p. 40—60°), passed in benzene solution through an alumina column, and recrystallised from light petroleum, forming colourless prisms, m. p. 107·5—108·5° (Found : C, 71·1; H, 7·4. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·4%). The ferric reaction in alcoholic solution was dark violet.

3′-Keto-6-hydroxy-2 : 5-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 2-cyclopentenonaphthalene-α (IX).—A mixture of the above keto-ester-α (5 g.), hydriodic acid (18 c.c., *d* 1·7), and acetic acid (30 c.c.) was refluxed for 3½ hours. The ethereal extract of the diluted solution was freed from iodine and acids and evaporated. The product was crystallised from benzene–light petroleum (b. p. 60—80°) (charcoal), sublimed at 160°/0·05 mm., and recrystallised from a little benzene. It was obtained in thick, white prisms, m. p. 189—191° (Found : C, 78·0; H, 7·9. $C_{15}H_{16}O_2$ requires C, 78·2; H, 7·9%). Starting with the monomethyl ester-α (from VII) (7 g.), the processes of homologation, ring-closure, and hydrolysis were also effected without isolation of intermediates and 3·6 g. (68·5% overall yield) of the hydroxy-ketone-α were obtained.

Similarly the related monomethyl ester-β (2·9 g.), by the same procedure, gave the hydroxy-ketone-β (0·5 g.). This substance was crystallised from methanol, sublimed at 200°/0·05 mm., and recrystallised from benzene. It formed thick, white prisms, m. p. 230—231° (Found : C, 78·2; H, 7·8%). Like equilenin, these hydroxy-ketones fuse to red liquids when heated in air. The m. p.'s were determined in evacuated sealed capillaries; colourless liquids then resulted. The β-form now melts at a higher temperature than the α, so the m. p. is no criterion of stereochemical configuration. Addition of *p*-nitrobenzenediazonium chloride to an alkaline solution of these phenolic ketones produces an intense violet-red coloration.

Use of Palladium–Strontium Carbonate as Catalyst in Pressure Hydrogenation.—(*a*) Phenol (30 g.) was reduced in dioxan (40 c.c.) in the presence of palladised strontium carbonate (5 g. of 2%). Starting at 20°/113 atms., after ½ hour, 75°/125 atms., after 1½ hours, 140°/125 atms., absorption ceased after 4 hours (150°). The yield of *cyclo*hexanol was almost quantitative.

(*b*) Quinol dimethyl ether was similarly reduced but for too short a period (1¾ hours, finally at 210°/94 atms.) owing to mechanical trouble. The product was separated into 1 : 4-dimethoxy*cyclo*hexane, b. p. 169—170°/15 mm., $n_D^{20°}$ 1·450, and unchanged material.

(*c*) Ethyl *p*-hydroxybenzoate (20 g.) was reduced in dioxan (40 c.c.) in the presence of the catalyst (4 g.). Initial conditions were 15°/118 atms.; after 40 minutes, 155°/150 atms.; after 2 hours, 157°/90 atms. and reduction ceased. The product, obtained in almost quantitative yield, was *trans*-4-carbethoxy*cyclo*hexanol, b. p. 255—256°, $n_D^{25°}$ 1·463. The crude acid obtained on hydrolysis had m. p. 115—117°, raised to 120—121° by one crystallisation. The pure *trans*-acid has m. p. 121° and the *cis*-acid, m. p. 152° (Perkin, *loc. cit.*; Balas and Srol, *loc. cit.*). Oxidation of this *sec.*-alcohol (10 g.) by means of chromic acid (10% excess) in acetic acid solution for ½ hour at 0° and 18 hours at room temperature afforded 8·4 g. of 4-carbethoxy*cyclo*hexanone, b. p. 150—152°/40 mm.

The dioxan employed must be pure and in some cases reduction did not occur below 180—190°. Furthermore the catalyst loses activity when heated in the solvent under hydrogen without stirring. The reduction must therefore not be stopped and resumed later, and stirring must be continuous. Dr. E. Seijo (private communication) has recently found that ethyl acetate is a very satisfactory solvent for this reduction at about 140—150°/140 atms. Ethyl *p*-hydroxybenzoate may be used as a test substance to ensure that catalyst and solvent are in good condition. Using Raney nickel, reduction was very slow and far from completed after 6 hours at 200°/168—128 atms.

(*d*) The phenolic dimethyl ester-α (VII, R = H) was not reduced in dioxan after 4 hours at 180—200°/165 atms., or in methanol at 200°/160 atms. The substance was recovered unchanged.

3′ : 6-*Dihydroxy*-2 : 5-*dimethyldecahydro*cyclo*pentenonaphthalene* (*Stereoisomerides of α-Series*) (X).—The phenolic ketone (*a*) (2 g.) was hydrogenated in dioxan (70 c.c.) in the presence of palladised strontium carbonate (0·8 g.). Starting at 20°/93 atms., the conditions after 1 hour were 196°/134 atms.; after 2 hours, 227°/142 atms. for a few minutes; 202°/133 atms. was maintained for 3½ hours. The solvent was removed, and an ethereal solution of the product washed with aqueous sodium hydroxide (10%); phenols were not found in these washings. The material was distilled: (*a*) bath at 140°/0·05 mm., one or two drops of a colourless mobile oil (Found: C, 78·8; H, 11·3. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%); (*b*) bath at 140°/0·05 mm., a colourless glass (Found: C, 76·3; H, 10·9%); (*c*) bath at 145°/0·05 mm., a colourless glass (Found: C, 75·4; H, 10·9; active H in pyridine, 0·7%); (*d*) bath at 145—147°/0·05 mm., a colourless glass (Found: C, 75·7; H, 10·9. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0; 2H, 0·8%). There was no residue, (*b*) and (*c*) constituted each about ⅔ of the product and (*d*) about ⅓. It is apparent from these results that the yield of the desired products was almost quantitative. In a later experiment it was found that the temperature needed was 220° but, in this case also, hydrogenolysis of the alcoholic groups did not occur.

3′ : 6-*Diketo*-2 : 5-*dimethyldecahydro*-1 : 2-cyclo*pentenonaphthalene*-x-α(I).—The above di-*sec.*-alcohol of the α-series (1·5 g.) in acetic acid (40 c.c.) was treated at 10—15° with chromic anhydride (1·3 g.) in acetic acid (30 c.c.) and a few drops of water. After 24 hours at room temperature, a little methanol was added, and the solution concentrated under diminished pressure. Water was added, and an ethereal solution of the product washed with aqueous sodium carbonate and distilled. After the solvent the whole formed 3 fractions (2 : 2 : 1) of a colourless viscous oil: (*a*) bath at 130°/0·01 mm. (Found: C, 76·9; H, 9·7; active H, 0·08%); (*b*) bath at 135°/0·01 mm. (Found: C, 77·0; H, 9·6%); (*c*) bath at 140°/0·01 mm. (Found: C, 77·2; H, 9·6%). After a few days the substance partly crystallised in long prismatic needles; it could be recrystallised from light petroleum (b. p. 40—60°) (seeding) and separated in transparent, colourless prisms, m. p. 116—117° (Found: C, 76·9; H, 9·6. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·4%). The diketone has evidently been obtained largely in one stereoisomeric form (x-α). All the fractions afforded sparingly soluble, yellow dinitrophenylhydrazones, which have not yet been obtained in a pure condition and are mixtures of mono- and di-derivatives.

Unsaturated Ketones, $C_{15}H_{24}O_2$.—A mixture of the above diketone (1 g., not crystallised), powdered sodamide (1 g.), and ether (30 c.c.) was refluxed under nitrogen for 6 hours, then cooled in ice while a solution of 4-diethylaminobutan-2-one methiodide (from 1·2 g. of the base) in alcohol (8 c.c., and later 15 c.c.) was introduced. After ½ hour the mixture was kept at room temperature for 1½ hours and refluxed for 1½ hours, always under nitrogen. The cooled mixture was decomposed with ice and hydrochloric acid, and the ethereal layer washed with aqueous sodium thiosulphate, water, aqueous sodium carbonate and water, and dried. The ether was evaporated, and the residue distilled (temperatures are those of the bath): (*a*) 125—135°/0·05 mm., (*b*) 135—150°/0·05 mm., (*c*) 150—220°/0·05 mm., (*d*) appreciable residue; (*c*) gave (*e*) 135°/0·05 mm., (*f*) 150—180°/0·05 mm., (*g*) 180—190°/0·05 mm.; (*g*) gave (*h*) —185°/0·1 mm., (*i*) 185°/0·1 mm., a light yellow, very viscous oil (Found: C, 78·9; H, 9·7%), (*j*) 190°/0·1 mm., a similar viscous oil (Found: C, 79·2; H, 9·3%); (*f*) gave (*k*) 130—140°/0·05 mm., (*l*) 160—180°/0·05 mm.; (*l*) gave (*m*) —150°/0·05 mm., (*n*) 160—180°/0·05 mm., a light yellow, very viscous oil (Found: C, 79·0; H, 9·6%); (*d*) gave (*o*) —240°/0·1 mm., (*p*) small residue; (*o*) gave (*q*) 180—190°/0·05 mm., a yellow viscous oil (Found: C, 79·4; H, 9·0. $C_{15}H_{22}O_2$ requires C, 79·7; H, 9·2%), (*r*) 190°/0·05 mm. This survey shows that a tetracyclic compound has been formed in accordance with anticipations. The tricyclic starting point requires C, 76·9% and the pentacyclic, doubly unsaturated ketone, $C_{23}H_{30}O_2$, requires C, 81·6; H, 8·9%. The absorption in alcoholic solution (*c*, 1·08 × 10^{-4}) was kindly examined by Dr. F. B. Strauss; fraction (*j*) was employed. The characteristic band of an αβ-unsaturated ketone was observed; λ max., 2415 A., ε max., 11,500 (cf. Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123). The absorption of androstenedione is recorded as follows: Butenandt and Kudszus (*Z. physiol. Chem.*, 1935, **237**, 75), λ, 2350 for 0·01% solution in chloroform; Butenandt and Peters (*Ber.*, 1938, **71**, 2690), λ, 2400 for 0·02% solution in chloroform; Ruzicka and Wettstein (*Helv. Chim. Acta*, 1935, **18**, 986), λ 2350, solvent not specified; Hogness, Sidwell, and Zscheile (*J. Biol. Chem.*, 1937, **120**, 239), λ, 2408, in alcoholic solution. The investigation is being continued.

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133. *Experiments on the Synthesis of Substances related to the Sterols. Part XLII.*

By R. H. MARTIN and SIR ROBERT ROBINSON.

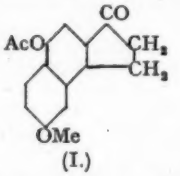
This communication records extensions of the work of Robinson (J., 1938, 1390) and Bateman and Robinson (J., 1941, 398) in the 3′-substituted *cyclo*pentenonaphthalene series. An improved preparation of 3′-keto-4-hydroxy-1 : 2-*cyclo*pentenonaphthalene is described, and its *methyl* ether (II, R = Me) submitted to the Reformatzky reaction with ethyl bromoacetate, and oxidised by means of selenium dioxide to an *α-diketone*. The latter reaction has also been applied to 3′-keto-4 : 6-dimethoxy-1 : 2-*cyclo*pentenophenanthrene, and the *diketone* oxidised to a *dicarboxylic acid*. 3′-*Keto*-4-*acetoxy*-7-*methoxy*-1 : 2-cyclo*pentenonaphthalene* (I) has been

obtained by the usual series of operations from *m*-methoxyacetophenone, but an attempt to prepare a 3′-keto-6-methoxy-5-methyl*cyclo*pentenonaphthalene derivative failed because one of the earlier processes in the synthesis took an abnormal course. Substances of the type mentioned would be valuable intermediates for the synthesis of analogues of progesterone and corticosterone.

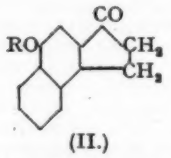
The hydrogenation of 4 : 6-dimethoxy-1 : 2-*cyclo*pentadienonaphthalene-3′-acetic acid has been re-investigated. It is shown that reduction occurs in the terminal aromatic nucleus.

BATEMAN and ROBINSON (*loc. cit.*) found that 3-*p*-methoxyphenyl-Δ^2-*cyclo*penten-1-one-2-acetic acid was readily cyclised by means of acetic anhydride at 170—190°. As the ring-closure occurred in the *m*-position to a methoxyl group, it occurred to us that migration was a possibility (cf. Hayashi, J., 1930, 1513) and in this case the product would have been 3′-*keto*-4-*acetoxy*-7-*methoxy*-1 : 2-cyclo*pentenonaphthalene* (I). The synthesis of this substance has proved that the punctilio was unnecessary.

The action of acetic anhydride on 3-phenyl*cyclo*pentenoneacetic acid affords 3′-*keto*-4-*acetoxy*-1 : 2-cyclo*pentenonaphthalene* (II, R = Ac) in good yield and the corresponding *methyl* ether (II, R = Me) yields (III) by the Reformatzky reaction, followed by hydrolysis and reduction. This *acid* was required as a reference



(I.)



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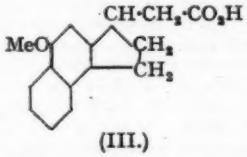
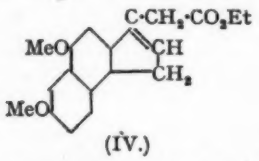


(III.)

compound in connexion with experiments on the hydrogenation of 4 : 6-dimethoxy-1 : 2-*cyclo*pentadienonaphthalene-3′-acetic acid (IV), already studied by Bateman and Robinson (*loc. cit.*). One of the main products isolated in the earlier work was an ester, m. p. 45—50°, which gave an acid, $C_{17}H_{22}O_4$, m. p. 117—118°. We have now found that this acid is a mixture (probably of stereoisomerides) and the main constituent ($C_{17}H_{22}O_4$) has m. p. 131—132·5° and the structure (V). On treatment with hydriodic acid and remethylation it yields



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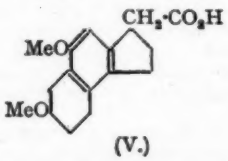

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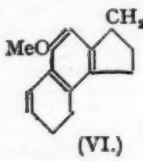

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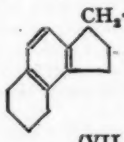
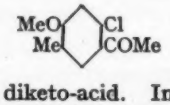


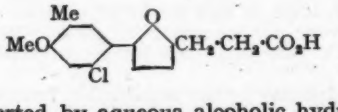
(VII.)

an *acid*, regarded as (VI), and this on dehydrogenation (by way of its ester) is converted into (III). The uncrystallisable acids obtained by hydrolysis of the hydrogenation product gave no pure compounds by direct separation. After dehydrogenation of the methyl esters and hydrolysis, an *acid*, believed to be (VII), was isolated. An alternative interpretation is mentioned below.

As an intermediate for 3′-keto-6-methoxy-5-methyl*cyclo*pentenonaphthalene we wished to have a ready source of 4-chloro-*o*-tolyl methyl ether and were led to investigate the nitration of *o*-tolyl carbonate in the hope that nitration would occur in the *p*-position to the methyl group. Copisarow (J., 1929, 588) had already shown that the nitration of *p*-tolyl carbonate proceeds in the *o*-position to the methyl group. However, in the case of *o*-tolyl carbonate, nitration occurs almost exclusively para to the oxygen, an interesting contrast.

We are grateful to Messrs. I.C.I. (Dyestuffs) Ltd. for a supply of 4-chloro-2-nitrotoluene, from which 4-*chloro*-o-*tolyl methyl ether* was prepared by standard methods. The Friedel–Crafts reaction then afforded 2-*chloro*-4-*methoxy*-5-*methylacetophenone* (VIII). The *furfurylidene* derivative of this ketone could not be hydrolysed

(VIII.) 



(IX.)

in the usual way to a diketo-acid. Instead it was converted by aqueous alcoholic hydrogen chloride into 2-(4′-*chloro*-6′-*methoxy*-m-*tolyl*)*furan*-5-β-*propionic acid* (IX). All attempts to open the furan ring failed and the projected synthesis could not be realised.

EXPERIMENTAL.

3′-*Keto*-4-*acetoxy*-1 : 2-cyclo*pentenonaphthalene* (II, R = Ac).—A mixture of 3-phenyl-Δ^2-*cyclo*penten-1-one-2-acetic acid (14·1 g.) (Robinson, *loc. cit.*) and acetic anhydride (60 c.c.) was heated in a stout sealed flask at 190° for 1 hour. On cooling, finally rapidly in ice-water, 11·65 g. of crystals, m. p. 156—158°, separated and 1·15 g. more were obtained by concentration of the mother-liquor. The *derivative* was crystallised from methanol, sublimed at 155°/0·3 mm., and recrystallised from methanol, forming thick white needles, m. p. 159—160° (Found: C, 74·9; H, 4·9. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·1%). On hydrolysis with aqueous alcoholic sodium hydroxide and acidification the corresponding phenol was obtained and this exhibited all the properties of the substance previously obtained by the much inferior process of cyclisation by means of sulphuric acid (*loc. cit.*). The corresponding *methyl* ether (II, R = Me) was prepared from both specimens and a mixture showed no depression of m. p. The acetate was treated with alcoholic potassium hydroxide and methyl sulphate until the yellow colour of the alkaline solution was quite faint. The substance (yield, almost quantitative) was crystallised from ethyl acetate, sublimed at 135°/0·3 mm., and crystallised from alcohol, being so obtained in small, white needles, m. p. 127·5—128·5° (Found: C, 79·4; H, 5·7. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%).

The solution in sulphuric acid had a bright yellow colour. The dark red 2 : 4-*dinitrophenylhydrazone* of the methyl ether separated from xylene in microscopic crystals, m. p. 301° (Found : C, 61·3; H, 4·3. $C_{20}H_{16}O_5N_4$ requires C, 61·2; H, 4·1%).

4-*Methoxy*-1 : 2-cyclo*pentadienonaphthalene*-3′-*acetic Acid*.—A mixture of ketomethoxy*cyclo*pentenonaphthalene (3 g.), ethyl bromoacetate (4·8 g.), zinc ribbon (2·6 g.), and benzene (45 c.c.) was refluxed for 2 hours and then decomposed with ice and hydrochloric acid. The benzene layer was freed from acids, dried, and evaporated, and the residual yellowish-brown cake crystallised from methanol (yield, 2·9 g.). The yellow colour can be removed by means of alumina or charcoal. For analysis the *substance* was sublimed at 120°/0·05 mm. and crystallised twice from methanol; it formed white needles, m. p. 123—123·5° (Found : C, 76·9; H, 6·8. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·5%). Hydrolysis with methanolic sodium methoxide, followed by gradual addition of water, and later, hydrochloric acid, gave the corresponding *acid*, which was twice crystallised from a little acetone (refrigerator), sublimed at 190°/0·01 mm., and recrystallised from acetone It formed minute, colourless needles, m. p. 226—228° (decomp.) (Found : C, 75·5; H, 5·8. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%).

4-*Methoxy*-1 : 2-cyclo*pentenonaphthalene*-3′-*acetic Acid* (III).—The above ester (1·9 g.) in methanol (30 c.c.) was hydrogenated at 18°/2 atms. for 8 hours in the presence of palladised strontium carbonate (1·2 g. of 2%). The product distilled (bath at 190—200°/0·15 mm.) as a very pale yellow oil (1·8 g.) which did not crystallise on keeping at 0°. It was hydrolysed by refluxing with methanolic potassium hydroxide and a few drops of water. The *acid* was isolated in the usual way, twice crystallised from aqueous acetic acid, sublimed at 150°/0·5 mm., and recrystallised from aqueous methanol. It formed colourless prismatic needles, m. p. 132—137°, containing solvent; it was therefore resublimed, m. p. 136—137·5° after slight sintering (Found : C, 75·1; H, 6·2. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%).

2′ : 3′-*Diketo*-4-*methoxy*-1 : 2-cyclo*pentenonaphthalene*.—A mixture of ketomethoxy*cyclo*pentenonaphthalene (1 g.), selenium dioxide (0·5 g.), and acetic acid (15 c.c.) was boiled for 3 minutes, mixed with a little water, and cooled. The precipitated *product*, thrice crystallised from acetone, formed yellow, microscopic prisms, m. p. 178—180° (Found : C, 73·7; H, 4·3. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·5%).

Furfurylidene-3-*methoxyacetophenone*.—Following the elegant method of Claisen for the preparation of ethyl benzoylacetate, *m*-methoxybenzoyl chloride (54 g., from thionyl chloride and the acid) and ethyl acetoacetate (41·2 g.) were used; the successive hydrolyses were effected by means of 10% aqueous ammonia and boiling 10% aqueous sodium hydroxide. The ketone, b. p. 138—139°/24 mm. (yield, 32·6 g. or 68·5%), gave a semicarbazone, m. p. 195—197° after crystallisation from dioxan, these data being in agreement with the records (cf. Wahl and Silberzweig, *Bull. Soc. chim.*, 1912, **11**, 61). The condensation with furfuraldehyde (1 mol.) was carried out in cold methanolic solution containing 1% of sodium methoxide; the product, collected by means of ether, distilled as a light yellow oil, b. p. 185°/0·6 mm. (yield, 92%). A redistilled specimen, b. p. 175°/0·45 mm., solidified in the ice-chest. The *substance* crystallised from light petroleum (b. p. 60—80°) (charcoal) in small, pale yellow needles, m. p. 38·5—39·5°, which became brownish-red on keeping (Found : C, 74·2; H, 5·7. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%). Analysis of several specimens failed to give sharper figures. The solution in sulphuric acid had a deep red colour and the dark red 2 : 4-*dinitrophenylhydrazone*, crystallised from acetic acid, had m. p. 190—191° (Found : C, 58·8; H, 4·0. $C_{20}H_{16}O_6N_4$ requires C, 58·8; H, 4·0%). Following the usual procedure (Kehrer and Igler, *Ber.*, 1899, **32**, 1178; Robinson, *loc. cit.*) the furfurylidenemethoxyacetophenone gave 4 : 7-*diketo*-m-*methoxyphenylheptoic acid*, which, crystallised from water containing a little acetic acid (charcoal), formed white needles, m. p. 87—88° (Found : C, 63·9; H, 5·9. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%).

3′-*Keto*-4-*acetoxy*-7-*methoxy*-1 : 2-cyclo*pentenonaphthalene* (I).—The above diketo-acid was cyclised as usual by boiling 2% aqueous potassium hydroxide; the product was a yellow oil (21·5 g. from 60 g. of furfurylidenemethoxyacetophenone). The substance crystallised with some difficulty from ethyl acetate–light petroleum in the refrigerator and was recrystallised successively from benzene, ethyl acetate, and benzene. 3-m-*Methoxyphenyl*-Δ^2-cyclo*penten*-1-*one*-2-*acetic acid* formed thick, colourless prisms, m. p. 100—101° (Found : C, 68·1; H, 5·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·8%). The crude acid (15 g.) was boiled with acetic anhydride (25 c.c.) for 1½ hours, and, on rapid cooling, 10·6 g. of a nearly white powder separated. The *substance* was crystallised from alcohol, aqueous acetic acid, dioxan, and finally from alcohol and obtained in white needles, m. p. 177·5—178° (Found : C, 71·3; H, 4·9. $C_{14}H_{14}O_4$ requires C, 71·1; H, 5·2%). The solution in sulphuric acid was yellow and by hydrolysis a phenol was obtained which dissolved in alkali to a yellow solution and coupled with *p*-nitrobenzenediazonium salts to a red azo-compound. The original mother-liquor contained a more readily soluble isomeride, evidently 3′-*keto*-4-*acetoxy*-5-*methoxy*-1 : 2-cyclo*pentenonaphthalene*, which was obtained in a pure condition only after a laborious series of fractional crystallisations from alcohol, dioxan, methanol and ether, as well as passage of a solution in benzene through an alumina column. In this way 1·3 g. of the 7-methoxy-compound and 0·3 g. (m. p. 192—196°) of the 5-methoxy-compound were isolated. The latter was sublimed at 170—180°/0·1 mm., crystallised twice from methanol, and sublimed again, forming white needles, m. p. 196·5—198° (Found : C, 70·7; H, 5·2. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%). The following mixtures showed large depressions of m. p. : 6-MeO, 7-MeO; 6-MeO, 5-MeO; 7-MeO, 5-MeO.

Hydrogenation of 4 : 6-*Dimethoxy*-1 : 2-cyclo*pentadienonaphthalene*-3′-*acetic Acid* (cf. Bateman and Robinson, *loc. cit.*).—There is not much real evidence in regard to the position of the double bond in this ester. Other things being equal, an indene structure would be anticipated, but it was described as a yellow substance and this favoured an exocyclic constitution. We have now found that the colour is due to an impurity which cannot be removed by crystallisation. Sublimation in a high vacuum afforded a colourless product which crystallised in white needles of unaltered m. p. The ester (10 g.) was reduced under the same conditions as heretofore, except that the solvent (alcohol) was reduced to 60 c.c. and the time of reaction to 10 hours. After hydrolysis with alcoholic potassium hydroxide, and crystallisation of the resulting acid from benzene–light petroleum (b. p. 60—80°), 3·6 g., m. p. 117—118°, were isolated and the material was identical with that previously obtained, for which analysis indicated the formula $C_{17}H_{22}O_4$. Under milder conditions (145—150°/125 atms.) the acid, produced in equal yield, had m. p. 124—125°, raised to 131—132·5° by crystallisation from benzene–light petroleum (Found : C, 70·1; H, 7·6. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%). It was then found that the m. p. of the acid, m. p. 117—118°, could be raised to 129° by fractional crystallisation. In one case a mixture of needles and plates separated, but these, when hand-picked, showed the same m. p. and mixed m. p. The m. p. of mixed fractions was always between the values for the constituents. Taking into account the analytical data and the chemical behaviour of the material, m. p. 117—118°, there can be no doubt that it is a mixture of closely related stereoisomerides. It is shown below that the constitution is that of 4 : 6-*dimethoxy*-5 : 6 : 7 : 8-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-3′-*acetic acid* (V), which should occur in two inactive stereoisomeric forms. The rings should be co-planar and very little is known of the physical behaviour of mixtures of stereoisomerides in which the groups responsible for *cis-trans*-configurations are so far removed from one another in the molecule. A mixture of the acids (2 g., m. p. 117—118°), hydriodic acid (7 c.c., *d* 1·7), and acetic acid (7 c.c.) was refluxed for ½ hour. The product was isolated by means of ether and freed from iodine; it formed a greenish solid and was at once methylated by means of methyl sulphate (10 c.c.) and potassium hydroxide in aqueous methanol. The isolated, acidic product was sublimed at 150°/0·0025 mm. (0·6 g.). It separated from aqueous acetic acid in white, microscopic crystals and was then resublimed, m. p. 154·5—156·5° (Found : C, 74·0; H, 7·4. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%). The acid absorbs bromine in chloroform solution without

liberation of hydrogen bromide and its ester may be dehydrogenated with unusual ease (see below). It is therefore certainly a dihydronaphthalene derivative and almost certainly 4-*methoxy*-7 : 8-*dihydro*-1 : 2-cyclo*pentenonaphthalene*-3'-*acetic acid* (VI).

In order to avoid loss of carbon dioxide, the sublimed acid (0·6 g.) was esterified with ethereal diazomethane from 2 c.c. of nitrosomethylurethane; the derivative was an oil which later crystallised, but was not further investigated. It was heated with palladised charcoal (0·1 g.) under nitrogen and hydrogen was evolved at 180°. To ensure completion of the reaction the mixture was heated at 300° for 2½ hours. After hydrolysis of the product the acid was sublimed at 140°/0·0025 mm., crystallised from aqueous methanol, and resublimed, m. p. 135° and m. p. 136—136·5° when mixed with an equal quantity of pure 4-methoxy-1 : 2-*cyclo*pentenonaphthalene-3'-acetic acid, m. p. 136—137°. The oxygen eliminated in the treatment with hydriodic acid is therefore that of the 6-methoxyl group and, further, this group is situated in the hydrogenated nucleus.

The uncrystallisable acids in the mother-liquors from the acids, m. p. 117—118° and m. p. 124—125°, were twice distilled, b. p. 160—167°/0·03 mm. The analyses were not satisfactory (*e.g.*, Found : C, 76·3; H, 8·9%) and indicated complex mixtures of substances that have suffered loss of one and two oxygen atoms. The mixture was heated with palladised charcoal under nitrogen; carbon dioxide was evolved below 150°. The temperature was maintained at 280° for 8 hours. On working up, a neutral product, b. p. 180—200°/17 mm., was obtained as a clear, mobile oil, $n_D^{20°}$ 1·6005 (Found : C, 87·6; H, 7·9%). We interpret this as a mixture of $C_{14}H_{14}$ and $C_{15}H_{16}O$. In order to avoid decarboxylation the distilled oily acids were esterified with diazomethane, and the ester heated with palladised charcoal under nitrogen. Evolution of gas started at 140—150° and the temperature was raised to 220° during 2 hours and maintained for 1 hour more. The resulting ester was hydrolysed, and the *acid* crystallised from benzene–light petroleum (b. p. 60—80°) and then many times from aqueous methanol and aqueous acetic acid. It was obtained in white plates, m. p. 109·5—111·5° (Found : C, 78·2; H, 7·4. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9%). There was a large depression of m. p. on admixture with the naphthalenoid acid, m. p. 136—137°, and a dihydronaphthalene would be most unlikely to resist the dehydrogenation process. Indeed it is curious that the tetralin derivative (VII) can do so and an alternative possibility is that the *cyclo*pentane ring is opened by the reduction at 3' : 2' or 3' : 4'. For example, in the former case the acid would be δ-1-naphthylvaleric acid ($C_{15}H_{16}O_2$ requires C, 78·9; H, 7·0%). The oily acids in the mother-liquor had b. p. 205°/0·03 mm. (Found : C, 76·4; H, 8·4%). We can reach no conclusion from these figures. Some crystals which separated after several months were not further investigated.

o-*Tolyl Carbonate.*—Einhorn and Hollandt (*Annalen*, 1898, **301**, 95) prepared the substance (m. p. 60°, analysis) by the action of carbonyl chloride on a pyridine solution of *o*-cresol. Subsequently the literature of the subject has been much confused. Barrel and Morel (*Bull. Soc. chim.*, 1899, **21**, 727) claim that they obtained the carbonate by distillation of *o*-tolyl chloroformate (b. p. 114°/25 mm.) at the ordinary pressure and give m. p. 80°, but no analysis. Copisarow (J., 1929, 588) passed carbonyl chloride into a solution of *o*-cresol in aqueous sodium hydroxide at 70—75° and reported an 85% yield of *o*-tolyl carbonate, a colourless oil (no analysis).

We have repeated this preparation and obtained the oil, which was readily separated into two fractions. From 108 g. of *o*-cresol we obtained 55 g., b. p. 84°/15 mm., and 50 g., b. p. 144—145°/0·5 mm. The latter fraction solidified and, after several crystallisations from alcohol and methanol, had m. p. 57—57·5° (Found : C, 74·3; H, 6·1. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8%). The first fraction contained chlorine and should be *o*-tolyl chloroformate. Its behaviour was quite different from that recorded by Barrel and Morel (*loc. cit.*) because it was recovered unchanged after refluxing for 2 hours at the ordinary pressure. On the other hand, it was converted into *o*-tolyl carbonate in almost quantitative yield on treatment with pyridine in benzene solution.

Nitration. Copisarow's method (*loc. cit.*) for *p*-tolyl carbonate was followed in essentials. The nitration of 10 g. was effected by nitric acid (4·8 c.c., *d* 1·43) and sulphuric acid (33 c.c. in all) first at −15°, then at −10° and finally at 0°. The product was hydrolysed by means of boiling aqueous potassium carbonate (22 g. in 150 c.c.), acidified, and steam-distilled. Slender yellow needles (0·3 g.) of 3-nitro-*o*-cresol, m. p. 69° (Gibson, J., 1925, **127**, 42, gives m. p. 70°), were collected from the distillate after the first few minutes and no more was obtained later. The main product was isolated by means of ether and distilled, b. p. 132°/0·2 mm. (9·2 g.). After crystallisation it formed faintly yellow needles, m. p. 82—84° and was identified as 5-nitro-*o*-cresol (Spiegel, Munblit, and Kaufmann, *Ber.*, 1906, **39**, 3240, give m. p. 82—85°). 4-Nitro-*o*-cresol was obtained in another experiment (final temperature 10°) and separated (0·3 g.) on acidification of the solution of the hydrolysed products. It formed cream needles, m. p. 116—117° (Ullmann and Fitzenkam, *Ber.*, 1905, **38**, 3787, give m. p. 118°). Thus there is evidence of the formation of small relative amounts of the carbonate of 3- and 4-nitro-*o*-cresols, but 5-nitro-*o*-cresol, a derivative of *p*-nitrophenol, constitutes more than 90% of the product.

Furfurylidene-6-*chloro*-4-*methoxy*-3-*methylacetophenone.*—Zinc dust (120 g.) was added with shaking to a solution of 4-chloro-2-nitrotoluene (50 g.) in acetic acid (500 c.c.), and the mixture refluxed for 1 hour. The resulting base (yield, 70%) was isolated in the known manner; b. p. 111°/9 mm., m. p. 20—21°, in agreement with Goldschmidt and Hönig (*Ber.*, 1886, **19**, 2440). 4-Chloro-*o*-toluidine sulphate (164·5 g.) was made into a paste with water (600 c.c.) and sulphuric acid (100 c.c.) and diazotised at 8—10° by addition of sodium nitrite (60 g.) in water (150 c.c.). One-third of the solution was slowly added to water (500 c.c.) and sulphuric acid (80 c.c.) while a rapid current of steam was passed. The other two-thirds were treated in the same way. From the distillates, 109 g. of 4-chloro-*o*-cresol were collected, m. p. 72° after crystallisation from light petroleum (b. p. 40—60°) (Zincke and Preiss, *Annalen*, 1918, **417**, 207, give m. p. 73—74°). Methylation by means of methyl sulphate and potassium hydroxide gave 90·5 g. of 4-chloro-*o*-tolyl methyl ether, b. p. 91—92°/13 mm. A solution of this (88 g.) and acetyl chloride (50 c.c.) in carbon disulphide (100 c.c.) was gradually added to a well-stirred suspension of aluminium chloride (85 g.) in carbon disulphide (250 c.c.) with cooling in ice-water. After 2 hours, the mixture was kept at room temperature for 2 hours and then refluxed for 3 hours (50 c.c. more carbon disulphide). The product (108 g. or 97%) had b. p. 158—160°/18—19 mm. It crystallised from light petroleum (b. p. 40—60°) in white needles, m. p. 45·5—46° (Found : C, 60·0; H, 5·5. $C_{10}H_{11}O_2Cl$ requires C, 60·4; H, 5·6%). A mixture of 6-*chloro*-4-*methoxy*-3-*methylacetophenone* (VIII) (100·5 g.), furfuraldehyde (43·5 c.c.), and methanol (100 c.c.) was stirred while methanolic sodium methoxide (0·85 g. of sodium in 85 c.c.) was gradually introduced. The *product* crystallised after about an hour and was collected after 12 hours (118 g., m. p. 77—78°). The derivative crystallised from light petroleum (b. p. 60—80°) in light yellow plates, m. p. 78—79° (Found : C, 65·1; H, 4·8. $C_{15}H_{13}O_3Cl$ requires C, 65·1; H, 4·8%).

2-(4'-*Chloro*-6'-*methoxy*-m-*tolyl*)*furan*-5-β-*propionic Acid* (IX).—A mixture of the above furfurylidene derivative (135 g.), alcohol (1·5 l.), and concentrated hydrochloric acid (400 c.c.) was refluxed for 18 hours. The alcohol was distilled under diminished pressure and the residual gum was separated and extracted repeatedly with boiling mixtures of acetic acid (200 c.c.), concentrated hydrochloric acid (100 c.c.), and water (150 c.c., finally reduced to 100 c.c.). A brownish crystalline powder separated on cooling (total, 41·6 g.). In all other cases so far examined, this procedure affords aryldiketoheptoic acids but in this example the related *furan* is the sole product. The substance was thrice crystallised from aqueous dioxan (charcoal), sublimed at 160°/0·005 mm., and crystallised from dioxan and from ethyl acetate. It formed faintly yellow needles, m. p. 175—177° after slight sintering (Found : C, 61·4; H, 5·5. $C_{15}H_{15}O_4Cl$ requires C, 61·1; H, 5·2%). The sodium salt is very sparingly soluble. The *methyl* ester was prepared by treatment with boiling saturated

methanolic hydrogen chloride (in the hope that the furan ring might be opened) and crystallised twice from light petroleum and then from aqueous acetic acid (charcoal). It formed colourless needles, m. p. 77—78° (Found : C, 62·8, 62·8; H, 5·6, 5·6; Cl, 11·5. $C_{16}H_{17}O_4Cl$ requires C, 62·2; H, 5·6; Cl, 11·4%). The derivative was also obtained by esterification of the acid with diazomethane.

2′ : 3′-Diketo-4 : 6-dimethoxy-1 : 2-cyclopentenonaphthalene.—When a mixture of 3′-keto-4 : 6-dimethoxy-1 : 2-*cyclo*pentenonaphthalene (Bateman and Robinson, *loc. cit.*) (5 g.), acetic acid (50 c.c.), and selenium dioxide (5 g.) was raised to the b. p., a vigorous reaction set in; it proceeded without further heating. When it had subsided, the solution was boiled for 1 minute, acetic acid (150 c.c.) added, and the mixture boiled for 2 minutes and filtered. Water (50 c.c.) was added, and the orange solid collected after cooling (4·7 g.). The *diketone* crystallised from acetic acid in deep brownish-orange needles, m. p. 243—245° (decomp.) (Found : C, 70·0; H, 4·9. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%). The solution in sulphuric acid had an intense brownish-crimson colour. The deep yellow *quinoxaline* derivative obtained with *o*-phenylenediamine crystallised from acetic acid–alcohol in needles, m. p. 247° (Found : C, 76·5; H, 5·0; N, 8·4. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·9; N, 8·5%). It formed a red, sparingly soluble hydrochloride and gave a blue solution in sulphuric acid. The yellow solution in toluene fluoresced blue.

2-Carboxy-4 : 6-dimethoxynaphthalene-1-acetic Acid.—A mixture of the above diketone (3·0 g.), water (25 c.c.), 10% sodium hydroxide solution (20 c.c.), and hydrogen peroxide (15 c.c. of 20 vol.) was gently heated with stirring and then raised to the b. p. in 5 minutes. After addition of 10% sodium hydroxide solution (10 c.c.) and hydrogen peroxide (10 c.c. of 20 vol.) the mixture was allowed to cool and then boiled for 5 minutes. On acidification of the filtered solution, 2·9 g. of the *acid* separated. The orange residue was probably a self-condensation product of the diketone; it dissolved in sulphuric acid to an opaque blue-black solution. The acid was readily soluble in acetone and crystallised from acetic acid in colourless aggregates of microscopic needles and flat, elongated, prismatic needles, m. p. 255—257° (decomp.) (Found : C, 58·0; H, 5·2. Found in material dried at 110° in a high vacuum : C, 61·9; H, 5·0. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%. $C_{15}H_{14}O_6$ requires C, 62·1; H, 4·8%).

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Dyson Perrins Laboratory, Oxford University. [*Received, August 4th*, 1943.]

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134. β-*Alkylation of Certain Kationoid Systems by Means of Grignard Reagents.*

By A. J. Birch and Sir Robert Robinson.

We are interested in the β-alkylation of αβ-unsaturated ketones and the like in connexion with the synthesis of long-chain aliphatic compounds containing a quaternary carbon atom (cf. J., 1942, 488) and as a means of introduction of the angle-methyl group of substances analogous to the sterols A few typical cases have been examined in order to estimate the scope of the reaction in relation to our problems.

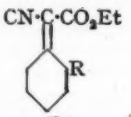
It is well known that the anionoid alkyl of a Grignard reagent often attacks the β-position of a double bond conjugated with a carbonyl, cyano-, or carbethoxyl group, but these groups can also enter into reaction, and the products formed vary with the conditions and even slight variations in structure (cf. Colonge, *Bull. Soc. chim.*, 1935, **2**, 754; 1936, **3**, 413). A possible cause of otherwise inexplicable contrasts which are recorded in the literature of the subject was revealed when Kharasch and Tawney (*J. Amer. Chem. Soc.*, 1941, **63**, 2308) demonstrated the important part played by traces of certain metal ions. It was found that the keto-group of *iso*phorone was normally the site of reaction (cf. Whitmore and Pedlow, *ibid.*, p. 758) but that in the presence of cuprous chloride, addition to the double bond predominated. We have found that carvone behaves similarly, since methylmagnesium iodide, in the presence of cuprous bromide, added almost exclusively to the endocyclic double bond, although Rupe and Liechtenhan (*Ber.*, 1906, **39**, 1122) and Klages (*ibid.*, p. 2310) found that the keto-group was attacked under the usual conditions.

Applying this reaction to 2-keto-$\Delta^{1:9}$-octalin, we obtained a 60% yield of *cis*-2-keto-9-methyldecalin. The configuration of the product was determined by the fact that it gave a homogeneous, crystalline oxime in more than 90% yield and the ketone was oxidised to *cis*-1-methyl*cyclo*hexane-1 : 2-diacetic acid, an authentic sample of which was kindly supplied by Dr. A. L. Walpole. This synthesis is more convenient than that of Linstead, Millidge, and Walpole (J., 1937, 1140) and constitutes a model for possible applications in the steroid field; owing to the production of the *cis*-configuration it is perhaps of greater potential value in relation to the polyterpenes.

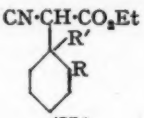
It appeared that *trans*-junction of the rings might result from the steric effect of a group, such as carbethoxyl, in position 10, which might subsequently be removed. The presence of such a group would also be expected to oppose the addition, and in order to see if it would still proceed, the action of methylmagnesium iodide, in the presence of cuprous bromide, on 2-keto-10-methyl-$\Delta^{1:9}$-octalin was examined. The ketonic product was isolated as *semicarbazone*, hydrolysis of which gave a substance which may be trans-2-*keto*-9 : 10-*dimethyldecalin*; the rather indefinite melting point indicated that it was not stereochemically homogeneous and the yield was unsatisfactory.

In the hope of obtaining intermediates which might be cyclised to *trans*-decalins or hydrindanes with a keto- or carboxyl group in the 1-position, required for projected steroid syntheses, attention was turned to the action of Grignard reagents on alkylidene cyanoacetic esters. Dialkylated cyanoacetic esters do not react with the Grignard reagents, so side reactions with the ester and cyano-groups should be avoidable. Kohler and Reimer (*Amer. Chem. J.*, 1905, **33**, 352) have added Grignard reagents to the double bond in compounds of the type of benzylidenecyanoacetic ester, so it seemed highly probable that they would add to compounds

of type (I). In fact, (I, R = H) added both *n*-decylmagnesium bromide and methylmagnesium iodide, giving (II; R = H, R′ = $C_{10}H_{21}$, Me). The product of the latter reaction was hydrolysed by means of aqueous alkali



(I.)



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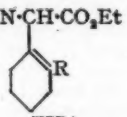

(III.)

to the malonamic acid, which was decarboxylated to 1-*methyl*cyclo*hexane*-1-*acetamide*. The yields in these two cases were 14% and 45% respectively and with (I, R = CH_3·CH_2·CO_2Et) the alkylation did not occur. The cause of the low yields was the isomerisation of (I) to (III), a type of transposition which is well known to be favoured by the alicyclic structure. In open-chain compounds the method may be more serviceable.

Experimental.

6-*Methylcarvomenthone*.—A solution of carvone (15·2 g.) in ether (40 c.c.) was slowly added to a stirred and ice-cooled Grignard solution from methyl iodide (16 g.) and magnesium (2·4 g.), containing cuprous bromide (0·1 g.). The mixture was refluxed for 10 minutes. The isolated product was heated with a crystal of iodine for 15 minutes at 180°, cooled, and, after removal of the trace of water, distilled, giving 2·5 g., b. p. *ca.* 200°, probably diene, and 11 g., b. p. 235—240° (Found: C, 79·1; H, 10·5. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·8%).

cis-2-*Keto*-9-*methyldecalin*.—2-Keto-$\Delta^{1:9}$-octalin (12 g.) was added to an ice-cooled and stirred Grignard solution (3 g. of magnesium and 19·5 g. of methyl iodide) containing cuprous bromide (0·2 g.). After an hour at room temperature the solution was refluxed for 15 minutes. It was decomposed with ice and dilute hydrochloric acid, and the ethereal layer separated and shaken with saturated aqueous sodium bisulphite for 3 hours. The liquid was filtered, and the solid washed with ether. The combined crystals and aqueous layer were acidified with hydrochloric acid, and heated on the steam-bath under reflux for 30 minutes. The product was a colourless oil with a pleasant camphoraceous odour, b. p. 250—254°, m. p. *ca.* 14·5° (Linstead *et al.*, 17—18°) (Found: C, 79·1; H, 10·7. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·8%).

The residue from the bisulphite extraction was distilled with a crystal of iodine, water being produced; on drying and redistillation 2·1 g. of an oil, b. p. 225°, were obtained. This is probably the diene, but was not further examined.

The ketone gave a semicarbazone, m. p. 212—213° (*ex* alcohol) (Linstead *et al.*, 211—212°), a 2 : 4-*dinitrophenylhydrazone*, pale orange needles from alcohol, m. p. 106° (Found: N, 16·8. $C_{17}H_{22}O_4N_4$ requires N, 16·2%), and a *benzylidene* derivative, pale yellow prisms from alcohol, m. p. 85—86° (Found: C, 84·2; H, 8·6. $C_{18}H_{22}O$ requires C, 85·0; H, 8·6%). The ketone (5 g.) gave the oxime (4·6 g.) as colourless prisms from alcohol, m. p. 109°; the mixture of isomerides at first produced was transformed into this variety after contact with aqueous alcoholic hydroxylamine hydrochloride for a week.

Oxidation with nitric acid by the method of Linstead *et al.* gave an acid, m. p. 192°, undepressed by admixture with an authentic specimen of *cis*-1-methyl*cyclo*hexane-1 : 2-diacetic acid, m. p. 192°.

2-*Keto*-9 : 10-*dimethyldecalin*.—2-Keto-10-methyl-$\Delta^{1:9}$-octalin (2·4 g.) in ether (15 c.c.) was slowly added to an ice-cooled and stirred Grignard solution from magnesium (0·5 g.) and methyl iodide (3·0 g.) in ether (20 c.c.), containing cuprous bromide (0·05 g.). After refluxing for 15 minutes the product was isolated and converted into a *semicarbazone*, which recrystallised from alcohol in colourless prisms, m. p. 202—203° (Found: C, 65·5; H, 9·5. $C_{13}H_{23}ON_3$ requires C, 65·9; H, 9·7%); yield, 120 mg. Steam distillation with dilute hydrochloric acid gave colourless prisms with a sweet camphoraceous odour, m. p. 90—95° (Found: C, 79·2; H, 10·9. $C_{12}H_{20}O$ requires C, 80·0; H, 11·1%).

Ethyl 1-n-*Decyl*cyclo*hexane*-1-*cyanoacetate*.—A Grignard solution from *n*-decyl bromide (25 g.) and magnesium (3 g.) in ether (40 c.c.) was slowly added to one of ethyl *cyclo*hexylidenecyanoacetate (15 g.) in ether (40 c.c.) with stirring and ice-cooling. After ½ hour the mixture was refluxed for 15 minutes. The product was isolated in the known manner and distilled. Following a fraction consisting of decane and unchanged ester, material, b. p. 200—235°/15 mm., was collected. On addition of alcohol eicosane was precipitated and collected. After removal of the solvent a pale yellow oil, b. p. 230—235°/15 mm., was obtained (yield, 14%) (Found: C, 75·1; H, 11·0. $C_{21}H_{37}O_2N$ requires C, 75·2; H, 11·0%).

Ethyl 1-*Methyl*cyclo*hexane*-1-*cyanoacetate*.—Ethyl *cyclo*hexylidenecyanoacetate (24 g.) in ether (50 c.c.) was brought into reaction as above with a Grignard solution from methyl iodide (19·5 g.) and magnesium (3 g.), but before distillation unchanged material was removed by treatment with an excess of cold aqueous alcoholic sodium cyanide for 1 hour. The *product* was an almost colourless oil, b. p. 155—160°/12 mm. (Found: C, 68·7; H, 9·0. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·1%); yield, 45%.

1-*Methyl*cyclo*hexane*-1-*acetamide*.—The above ester (5 g.) was refluxed with 15% aqueous sodium hydroxide for 3 hours, and the solution acidified. The precipitated acid (2·8 g.) crystallised from aqueous alcohol in plates, m. p. 151° (Found: C, 60·3; H, 8·4. $C_{10}H_{17}O_2N$ requires C, 60·3; H, 8·5%). This 1-*methyl*cyclo*hexane*-1-*malonamic acid*, when heated at 180° for 20 minutes, afforded a neutral *product*, which crystallised from alcohol in flat needles, m. p. 112—113° (Found: C, 69·3; H, 11·3. $C_9H_{17}ON$ requires C, 69·6; H, 11·0%).

Ethyl 2-β-*Carbethoxyethyl*-Δ^1-cyclo*hexene*-1-*cyanoacetate*.—A mixture of 2-β-carbethoxyethyl*cyclo*hexanone (9·9 g.), ethyl cyanoacetate (5·7 g.), and piperidine (3 drops) was heated on the steam-bath for 10 hours. Some unchanged ester and 5 g. of an oil, b. p. 150—153°/0·1 mm. (Found: C, 65·7; H, 8·1. $C_{16}H_{23}O_4N$ requires C, 65·5; H, 7·9%), were obtained.

After treatment with methylmagnesium iodide as above, the substance reacted almost completely with aqueous alcoholic sodium cyanide to give the water-soluble addition compound, so the double bond appears to be endo- rather than exo-cyclic.

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OBITUARY NOTICES.

RANDAL THOMAS MOWBRAY RAWDON BERKELEY, EARL OF BERKELEY.

1865—1942.

RANDAL THOMAS MOWBRAY RAWDON BERKELEY, eighth and last Earl of Berkeley, was head of a historic house which is one of the very few that can rightly claim a pre-Norman pedigree, tracing its descent from Eadnoth, a Saxon Thane, who was Staller to Edward the Confessor.

He was born in Brussels in 1865, and became Viscount Dursley in 1882 when his father succeeded his cousin in the Earldom. His mother was Cecile, daughter of Louis, Count de Melfort, whose ancestor John Drummond had followed James II into exile in France. He used to speak of his mother as having " a first-class reasoning mind " and this he certainly inherited from her. His parents lived abroad and he was educated at a lycée at Fontainebleau and later at Nice, until he came to England to be coached for the Navy, following the family tradition. He joined the *Britannia* in 1878, having passed in from Burney's Naval Academy at Gosport.

He quickly became an outstanding personality among his contemporaries. Above the average in physique, handsome, good at all games, he also took a high place in every examination, and was said to be " the best all-round man of our term." In those early days he was as wild as a hawk, ready to turn a back somersault off the mantelpiece for a bet and for any other physical feat of daring. His high spirits made naval discipline very irksome, and in spite of his promise as an officer he was often in trouble with their Lordships of the Admiralty. So it was no surprise to his friends when he left the Navy, although the immediate reason for this was his determination to do research.

He once told me that his interest in science and mathematics was first awakened during his school holidays before he joined the *Britannia* when he was taken to see Bidder, the " calculating phenomenon." Bidder was then an old man, but Berkeley was thrilled by his lightning calculations of engineering quantities, such as the number of bricks needed to build a complicated skew bridge over a river, and the deep impression made on the boy's mind was to bear abundant fruit. Years later his interest was stimulated again by a chaplain in one of the ships he served in who lent him books on chemistry which so inspired him that he decided to leave the Service and devote himself to science.

He resigned his commission in 1887 and in the same year he married the widow of Arthur Jackson. He then started to do chemistry at South Kensington under T. E. Thorpe, at the same time going to lectures in other subjects, including geology, to widen his knowledge. He wanted to choose his own line of research and this was not easy for a beginner, until a lecture on petrography by Judd aroused his interest in crystals, with the result that he began to study the relationship of crystal structure and chemical composition. Then a serious illness (double pneumonia) put an end to his work at South Kensington, and he was told that he could not winter again in England. However, he made a good recovery after a winter at St. Moritz and was able to take up research again on condition that he left London. So in 1893 he bought a house at Foxcombe on Boar's Hill just outside Oxford, and began his first experimental research in the Christ Church laboratory on an improved method of determining the density of crystals.

The work on crystal structure was abandoned when the investigations of Tutton, Pope and Barlow came on the horizon, but Berkeley always kept his interest in the phenomenon of crystallisation. Next came a research with Ernald Hartley in 1897 in the Balliol Laboratory (in the cellar on staircase XVI) on the electrolysis of glass, following on some work by Roberts Austen, and this turned his attention to semi-permeable membranes.

In 1898 he built a small laboratory at Foxcombe and began to plan a comprehensive attack on the application of van der Waals' equation to solutions, involving the determination of osmotic pressures. His first work there on the densities of saturated solutions was published in the *Philosophical Transactions* in 1904. The measurements were made with skill and accuracy and showed that he was gifted with an unusually fine sense of technique.

In 1902 the osmotic pressure work began in earnest when he was joined by Ernald Hartley, who was his collaborator until 1916 in this field. Berkeley was particularly fortunate in the choice of the first member of the Foxcombe team, as Hartley shared his own interest in accurate technique (his early work on mineral analysis had shown his manipulative skill) and his wide knowledge of chemical substances and his sagacity made him an invaluable partner in the osmotic pressure work.

Comparatively few osmotic pressures can be measured directly, and for such a comprehensive survey as Berkeley originally planned indirect methods must be used; hence his first goal was to check the accuracy of the indirect methods by direct measurement in some specified cases. This led him to a long series of researches pursued with great imagination and tenacity throughout his life, which remain to-day as the classical investigation in this field.

The new laboratory at Foxcombe was admirably planned and built for research in physical chemistry, and work started there in 1902 on the determination of the osmotic pressure of cane sugar solutions. The measurement of pressures running up to 150 atmospheres involved engineering design in which Berkeley showed real genius and he was well backed up by his mechanic Treeby, who carried out his ideas with great

skill. The semi-permeable membranes of copper ferrocyanide were formed on the outside of cylinders of Berlin porcelain, which were carried in a gun-metal vessel to which the necessary hydrostatic pressure could be applied to prevent the passage of water into the solution through the membrane. After many trials two almost perfect membranes were produced which served for all the work.

Simultaneously with these direct measurements the osmotic pressures were determined by the vapour pressure method due to Arrhenius. In this air is drawn first through the solutions and then through the pure solvent, when the lowering of the vapour pressure can be calculated from the losses in weight. It was soon found that the bubbling method was inaccurate, as the bubbles of air increased in size with the change in hydrostatic pressure and were never saturated, so a chain of vessels rocked in a thermostat was used in which the air passed over the surface of solution and solvent, thus practically eliminating the change in pressure across the apparatus. Even with this improvement the osmotic pressures calculated by the Arrhenius formula differed considerably from those determined directly. This turned Berkeley's attention to the thermodynamic cycle by which the Arrhenius equation was obtained, and he devised a more exact form of the expression, taking into account the variations of density with height of the columns, which brought the indirect values to within a few units per cent. of those directly measured. This was the start of his interest in thermodynamics, in which he became a great adept, particularly in the field of cyclic processes applied to solutions, an interest which continued unabated until his last paper of 1935. He was one of the first to insist on the importance of chemical thermodynamics in this country.

In 1907 Berkeley invited Charles Burton of the Cambridge Scientific Instrument Company to come to Foxcombe to help in the mathematical and instrumental sides of the work. Burton had already helped in the design of the apparatus made at Cambridge and had in fact suggested the general design of the osmotic pressure apparatus. He was in many ways a great addition to the team.

After Berkeley and Hartley had pointed out the main error in the Arrhenius equation, A. W. Porter had re-examined the thermodynamic cycle on which it was based and had derived an exact relationship between the osmotic pressure and vapour pressure lowering. The application of this involved the determination of the compressibility of the solutions and this was Burton's first work at Foxcombe. Berkeley had made a long search for ionised substances towards which the copper ferrocyanide membranes were semi-permeable in order to relate their osmotic pressure and dissociation, and in 1908 two papers appeared in the *Philosophical Transactions* on the osmotic pressure of calcium ferrocyanide which fulfilled this condition. In these the Porter equation, slightly modified, was applied for the first time and the direct and indirect determinations agreed to within 0·5%. Immense pains had been taken to improve the vapour pressure apparatus and eliminate every source of error.

The ionisation in such strong solutions was too complex a phenomenon to make the conductivity measurements of much significance, and the main result of this work was definitely to establish the validity of the exact equation for the indirect measurement of osmotic pressures, the primary goal at which Berkeley was aiming. However, the matter was not allowed to rest here and experiments were continued over the next eight years with new experimental refinements and a continuous search for sources of error in order to develop the most accurate and elegant methods of measuring osmotic pressures.

With the advent of Burton in 1907 the theoretical field was extended and a joint paper on the " Osmotic theory of solutions " two years later broke fresh ground in establishing the relationship between the two osmotic pressures in any liquid system of two components (or rather between their differential coefficients, a distinction to which Burton attached importance). Consideration of the differences in concentration due to gravitational attraction in the long columns of solution assumed to exist in the thermodynamic cycles applied to osmotic pressure led to a calculation of the changes in concentration produced by centrifugal force and an attempt to verify the result by experiment. I fancy that Berkeley always preferred the use of thermodynamic cycles to other methods because he felt that they kept him in close touch with physical realities and thereby enabled him to interpret the results and examine critically the assumptions on which they were based.

Van Calcar and de Bruyn had examined the changes in concentration produced by whirling a solution of cane sugar for four hours and taking samples at different points while the solution was in motion. Their results were irregular and far greater than theory predicted. Berkeley and Burton rotated narrow glass tubes containing a solution of cæsium chloride in a massive flat circular box of gun-metal at a speed of 57 revolutions per second for 243 hours and showed that the changes in concentration in the bottom, middle and top layers were of the same order as are required by theory. This was the beginning of a long and elaborate series of experiments on rates of diffusion and the stratification of centrifuged solutions in which Berkeley's ingenuity in devising new methods had full scope. Both investigations involved great experimental difficulties if they were to yield accurate results. The temperature of elaborate apparatus had to be maintained at a high degree of constancy for long periods, sometimes many days, to avoid convection currents. Samples had to be isolated at different points without risk of mixing, or the concentrations measured *in situ* by interferometer methods. Michelson, Fabry and Perrot, and Rayleigh instruments were all pressed into service for this purpose, but unfortunately the work was still in the experimental stage in 1914 and was never completed.

As the scope of the attack on the properties of solutions widened, the Foxcombe team had to be increased to meet the growing programme of research. M. P. Applebey (now Research Manager at Billingham) came to work on the boiling points of water and saturated solutions and on diffusion, J. W. Stephenson on the electrical conductivity of solutions, B. H. Wilsdon (now Director of Research at the Wool Industries Research Laboratory)

on diffusion and osmotic pressure in non-aqueous solvents, and D. E. Thomas on the partial pressures of the vapours of miscible liquids.

Meanwhile Berkeley's own mind was constantly at work trying to deduce from his results an equation of state for solutions, and to interpret the physical significance of osmotic phenomena. His paper in 1912 on "Solubility and supersolubility from the osmotic standpoint" shows the trend of his thoughts at this time. Starting with an analysis of the forms of the two osmotic pressure curves of two partially miscible liquids, he showed that at the concentrations where separation into layers occurs the form of the curves indicates a state of instability similar to that shown by the van der Waals curves where the separation of liquid from vapour occurs. He discusses in the light of this the conditions which would favour the separation of the new phase and the existence of a limit to the possible degree of supersaturation. He showed experimentally, following on the work of the American investigator Young, that the concentration at which crystallisation occurred in a supersaturated solution depended on the degree of mechanical shock to which it was subjected. This he explained as due to the setting up of compression-rarefaction waves in the solution, which brought it locally into the condition corresponding to a point of instability in his theoretical osmotic pressure curves.

In 1912 work at Foxcombe was in full swing and when Theodore Richards was in England to deliver the Faraday lecture I took him to spend the day with Berkeley. Richards was full of admiration for the laboratory and the two men were in immediate sympathy with one another, for they shared the same passion for accurate technique and the relentless pursuit of hidden errors. Few investigators fulfilled as well as Berkeley Richards' creed—

"First and foremost I should emphasise the overwhelming importance of perfect sincerity and truth; one must purge oneself of the very human tendency to look only at the favourable aspects of his work, and be ever on the look-out for self-deception (which may be quite unintentional). Each step should be questioned, and each possibility of improvement realised. And then, patience, patience! Only by unremitting, persistent labour can a lasting outcome be reached."

Those were the great days of the Foxcombe Laboratory, alas to end so abruptly with the war of 1914. Berkeley had chosen a fine well-balanced team and how good a leader he was can be seen from Applebey's sketch of the laboratory in the year he was working there—

"I went to work with Lord Berkeley," he says, "in 1910, when as you say he was in his most productive period. The great papers on the determination of osmotic pressure and vapour pressure had recently appeared, in which Berkeley had shown himself to be an experimenter of skill and imagination. The osmotic pressure work was, if not the first, surely the most notably successful of early applications of first-class engineering to the solution of experimental problems. The resource with which innumerable difficulties were overcome and the resolute rejection of all data on which the slightest suspicion could be thrown make this early work a model and an inspiration.

"When I got to Foxcombe, Berkeley's team already included Ernald Hartley, his invaluable and entirely reliable collaborator in the osmotic pressure work, and Charles Burton, a mathematical physicist of great and overflowing genius. The place was alight with enthusiasm and Berkeley's mind was stretching out in countless directions all radiating from his achievement in osmotic pressure. From cane sugar, one of the few solutes which was satisfactorily held by the copper ferrocyanide membrane, he turned to other sugars and glucosides, to the ferrocyanides of calcium and strontium and to the tetramethyl ester of ferrocyanic acid, itself only obtained by Hartley's painstaking and beautiful work, which incidentally revealed a new series of co-ordination compounds of great interest. All these were examined by the osmotic and vapour pressure methods. At the same time the investigation of osmotic properties by the boiling point method was ingeniously attacked, with particular attention to saturated solutions of salts. Berkeley's mind was much occupied from the outset I think with the problems of solubility and supersaturation. In his early papers he made too much effort to fit osmotic pressures to the model of the gas laws. He felt that osmotic pressure should obey some law of a modified van der Waals type, the discovery of which would give him the conditions of separation of the solute, just as van der Waals gives the conditions of separation of a condensate from a vapour. We shall all remember the patience and persistence with which he spent hours and days grinding out on the calculating machine trials of one empirical formula after another in the pursuit of this ignis fatuus. Nevertheless there was eventually notable fruit from this effort; thermodynamics was in his blood and was stimulated greatly by Burton, and the thermodynamic study of the solubility problem led him a few years later to what seems to me his most daring and greatest intellectual achievement, the great paper on "Solubility and supersolubility from the osmotic standpoint."

"It was impossible to be in Lord Berkeley's laboratory without being conscious of his intellectual powers. He was perhaps the better for not having passed through the common intellectual mill. He lacked some knowledge he might have acquired, but he was left with a very free mind. His speculations were ingenious, his imagination active and he never lost sight of the necessity for keeping his feet on the solid ground of experimental facts. Hating public discussion, he loved argument in his own circle. My most grateful recollection of him is the stimulation of the daily sessions at the blackboard when he would put up his ideas to be shot at. His ready ear for criticism, his anxiety to give credit to a younger colleague and his leaping mind made all this a stimulating period of my life for which I can never be too grateful."

During these years Berkeley's only other interest than science was golf, which he began to play under doctor's orders. Here again his instinctive grasp of scientific method and his application of it to anything

he took up soon had its effect. (He once spent a morning in the laboratory graduating a glass vessel to be used in his kitchen to standardise the making of mayonnaise !) He read most of the standard books on golf, he visited the famous courses and played with the best professionals, but their empirical methods did not satisfy him. So he set himself the problem of working out the dynamics of each type of shot and evolved his own methods. He laid out a nine-hole course at Foxcombe on novel principles to suit his own style and on this he was soon almost unbeatable. He would leave the laboratory in the afternoon, his caddie carrying a sack of golf balls and a mysterious bundle of canes. These were used for marking out new bunkers which sprang up most unexpectedly where his own practice shots never landed the ball, but sagaciously placed for the discomfiture of his visiting opponents. The greens were similar pitfalls for the unwary, being clothed with different kinds of grass and tended individually with special routine. The first, a peculiarly impossible hole, was known as Pa's Perk. Within a few years he made himself a scratch player and he entered twice for the Amateur Championship without, however, getting very far.

Lady Berkeley had died in 1898 and at Foxcombe he lived an almost monastic life, absorbed in research and golf. But visitors in those years will remember gratefully his step-daughter, Miss Sybil Jackson, who was his hostess, and particularly her most beautiful voice and rare gift for music.

After August, 1914, the team gradually dispersed to war work of various kinds, Burton to lose his life owing to an accident when engaged in war research, and Berkeley was left to gather up the threads of the osmotic pressure work that had been pursued unremittingly until then. One paper gave the final results of all the determinations made with Hartley by the direct method on both ionised and un-ionised solutions, and a second describes in detail the final experimental refinements of the vapour pressure method and the more exact thermodynamic equation used to calculate the osmotic pressures. The compressibilities had been redetermined by Burton by a more exact method. G. W. Walker, the Cambridge mathematician who came to Foxcombe in 1916, had made a fresh analysis of the Burton correction for the slight expansion of the air in passing from the solution vessel to the solvent vessel in the vapour pressure method. Every other source of error had been re-examined with truly meticulous care and any remaining inexactitudes in the method of calculation had been eliminated. The final tables of results showing the very close agreement of the values from the direct and the indirect determinations of osmotic pressure were a triumphal ending to Berkeley's work in this most exacting field and established finally the validity of his vapour pressure method. For cane sugar, for example, the values were—

Osmotic pressure of cane sugar solutions at 0°.

Concn. in g. per l.	56·50	81·20	112·00	141·00	183·00	217·50	243·00
O.P. measured directly	43·84	67·68	100·43	134·71	—	—	—
O.P. calc. from vapour pressure . .	43·91	67·43	100·53	134·86	186·86	230·70	264·46

Berkeley, however, was never satisfied and always striving after greater perfection, and until 1918 G. W. Walker continued Burton's theoretical investigation of the possible sources of error in the V.P. work, while Stenhouse took Hartley's place in the laboratory to investigate further refinements on the practical side. But whatever plans he may have had for resuming work at Foxcombe at the end of the war soon vanished on the death of his kinsman, Lord FitzHardinge, late in 1916, when he succeeded to Berkeley Castle and the Berkeley estates.

The Castle had been neglected for many years, it was in a sad state of repair, many of the walls being covered with ivy which had wrought havoc with the masonry. Parts of it had fallen into ruin even before Cromwell " slighted " it in 1639. Berkeley had always had a passion for building and his imagination was fired by the idea of restoring the Castle as far as possible to its original plan, and making it at the same time a beautiful home. For fourteen years it was his main occupation, and Berkeley Castle stands today as a " memorial to his taste, his sense of perfection and to that capacity for taking pains that is akin to genius, if it is not genius itself."

Among the ancestral responsibilities to which he succeeded in 1916 was the Mastership of the Berkeley Hounds. To the surprise of many he began hunting from the start, although he had practically no knowledge of horsemanship or of horses and was over fifty. However, with his usual determination he was soon able to acquit himself well and was generally up with hounds. This endeared him to his field, especially the farmers, who admired his pluck and dash.

Since leaving the Navy his life had been spent mainly at Foxcombe and Berkeley, but in 1924, after his marriage to Mrs. Lloyd, a daughter of the late John Lowell of Boston, U.S.A., much of his time was spent out of England. After he had given up the Mastership and the Foxcombe Laboratory was closed (1928) each winter was spent in Lady Berkeley's house at Santa Barbara in California, where he was immensely popular with a large circle of American friends, who admired his complete simplicity. He had taken up golf again and in his reach-me-down alpaca coat and old white canvas shoes he would beat the heads off smart young men who were many years his junior.

In the spring they always went to Italy, where Lady Berkeley was painting frescoes in a chapel at Assisi. They had taken a villa on a hilltop overlooking Rome, with a beautiful garden from which there was a glimpse of the dome of St. Peter's framed in an opening between the trees. Berkeley, as usual, was busy with additions and improvements, including the sound-proofing of the dining-room, previously notorious for its echoes.

June found them back at Berkeley for the summer to see their English friends, and many an hour was spent in his study discussing O.P. and V.P. and their future possibilities.

He started to play golf again in 1925 and made a short course at Berkeley. He also began to write a book on his own methods, which was published ten years later under the title of *Sound Golf by Applying Principles to Practice*. It contained the results of years of study of the easiest methods of playing shots. Berkeley divided golfers into " tigers," " goats " (" their heads much lighter than their nimbler heels ") and " rabbits," counting himself among the " goats " though he once had been a " tiger." His book was written for the " goat," the average golfer, to show him what he considered the simplest ways of playing different shots, which he had evolved by studying each of them as a problem in dynamics. I know of no other book which sets out in simple words the scientific analysis of the factors that affect the accuracy of each stroke. The " rabbits " who were his guests will recall how he tried to teach them his favourite shots like the " pinch " and the " poached egg."

However, in spite of all the new interests and excitements in his life, Berkeley never lost his affection for research and the problems of osmotic pressure were always in his mind. He was still anxious to perfect further the V.P. technique, so that it would be applicable to other solvents than water and to remove the last uncertainties in the calculation of osmotic pressures from the results. From 1916 until 1918 when he went to live at the Castle he continued to take an active part in the laboratory. The vapour pressure measurements had become more elaborate and exacting, and examining the effect of varying the experimental technique was a slow business, but Berkeley's patience was untiring. He worked harder than any one and was incessantly planning new refinements and improvements of technique. He worked quickly with deft manipulation and was never happier than when setting up new apparatus. Once when Stenhouse was lamenting that an analysis had taken more time than he had expected, Berkeley said characteristically, " Don't worry about that. The only thing that matters is accuracy. In our work we must behave as if we expected to live for ever."

Berkeley's main experimental interest in these years was to discover the deviations of the vapours of such common solvents as water, methyl and ethyl alcohols, and benzene from the gas laws so that the appropriate corrections might be applied in the O.P. calculations. This problem he attacked by measuring the relative losses from different liquids when the same air current passed over them, also the corresponding losses from the same liquid at different temperatures. After 1918 Stenhouse continued the work single-handed, but Berkeley followed it with the keenest interest, making frequent visits to Foxcombe when he was in England, and writing often several times a week when he was abroad. The work went on until the end of 1928 and I well remember the sad moment when the shafting stopped for the last time after supplying the motive power to so many brilliant experiments for nearly thirty years. The results, published in 1930 in a paper on " The density of the vapours in equilibrium with water, ethyl alcohol, methyl alcohol, and benzene," showed that there were deviations from the gas laws which were, however, difficult to interpret. Incidentally the experiments threw a good deal of light on the difficulties that would be encountered in applying the method he had elaborated so successfully for water to other solvents.

But though this was the end of his experimental work, which Berkeley never ceased to regret—he used to say that his happiest days were in the laboratory—his interest in osmotic pressure and osmotic phenomena continued to the end of his life. His calculating machine was never idle for long and letters and manuscripts used to arrive from California and Rome, with recalculations of his results, more exact thermodynamic equations, or suggesting new lines of attack. When he was in England there were long talks in his study at the Castle with the late Oliver Gatty, whose skilful help in the intricacies of thermodynamics Berkeley greatly valued.

His last two papers were published in the *Philosophical Magazine* in 1933 and 1935. The first was on an ingenious empirical equation by means of which the osmotic pressures of un-ionised aqueous solutions can be calculated from certain physical constants if one osmotic pressure is known. As usual there is a discussion of the physical significance of the equation, to which Berkeley's thoughts always turned. In trying to apply it to mixtures of alcohol and water he ran into difficulties. This turned his mind back to the Berkeley–Burton modification of the Porter equation for the osmotic pressures of solutions with two volatile constituents, and the object of his last paper on the general solution of this problem was to find the simplest means of applying this in practice. He once said that he was really more interested in mathematics than chemistry and his skilful treatment of some complex thermodynamic cycles showed that he had lost none of his old cunning in his seventieth year.

He died peacefully in his sleep on January 15th, 1942, and as he had no children by either marriage the romantic earldom of Berkeley ended with him.

HAROLD HARTLEY.

ALFRED ARCHIBALD BOON.

1866—1943.

THE death occurred in Edinburgh on April 1st, 1943, of Alfred Archibald Boon, D.Sc., B.A., F.I.C., F.R.S.E., Emeritus Professor of Chemistry in the Heriot-Watt College. He was unmarried and had been in failing health for some years.

Born in India, where his father was in the Indian Medical Service, Boon graduated B.A. at Madras University. He than came to Edinburgh University to study Chemistry under Crum Brown and Natural Philosophy under Tait, whose lectures appealed to him very strongly. He graduated B.Sc. in 1898, was awarded a Research Fellowship, and took the D.Sc. degree in 1905. His researches were in the field of Organic Chemistry; he was always keenly interested in the medical and pharmacological aspects of his subject.

For some years Boon was on the staff of one of the Training Colleges in Edinburgh and was also a part-time member of the Chemistry staff of the Heriot-Watt College. On two occasions, he conducted courses for teachers in Dublin on the invitation of the Board of Agriculture and Technical Instruction for Ireland. He soon became a full-time member of the staff of the Heriot-Watt College as lecturer in Organic Chemistry, Assistant Professor and, after the death of Professor John Gibson, he was appointed Professor of Chemistry in 1919, a post which he held until his retirement in 1931, with the title of Emeritus Professor.

Boon's research work was published in the *Journal* of this Society and in the *Journal* of the Pharmaceutical Society. He was interested in oxonium salts, particularly in the diarylidene-dimethylpyrones, which he found to be coloured basic compounds giving intensely coloured salts, and published several papers on this subject. Other investigations dealt with the reactions of pinacolone with ketols, such as benzoin, and with aldehydes. Amongst other topics which engaged his attention were aminoarsonic acids of the naphthalene series and the reaction between *mm'*-dinitrobenzil and diamines. In the latter case, he found that the reaction with benzidine or *o*-tolidine led to the formation not of a quinoxaline but of an additive compound between the two reactants. Based upon this fact, he devised a method, using benzidine, for the isolation of *mm'*-dinitrobenzil from the mixture resulting from the nitration of benzil. The writer can testify as to the scrupulous care taken by Boon in these investigations; he would not publish until he was completely satisfied with the accuracy of his results.

Boon was a very able teacher and took great care in the supervision and administration of his Department, which developed greatly under his direction, among the developments being courses in paper-making, brewing, and pharmacy. The interests of his Department and of his students came first, as many of his former students could testify. He never seemed to forget a student even after many years, and was always interested in their subsequent careers. The heavy administrative and teaching work he had to bear gave him little opportunities for research; in all his teaching he always stressed the great importance of fundamental principles.

During the last war, he undertook investigations for the Services, particularly for the Admiralty, such as the systematic examination of oils collected from the surface of the North Sea whenever a German submarine was destroyed, the first of these being at Fidra in the Firth of Forth. He also took part in work for the Ministry of Munitions.

On two occasions, Boon served on the Council of the Institute of Chemistry; he was for many years a Member of the Board of Examiners in Scotland of the Pharmaceutical Society of Great Britain, and served on several Committees dealing with the training of pharmacists, a question in which he was deeply interested.

A man of deep religious convictions, Boon was a hater of injustice, was very conscientious, fair minded, and helpful to any who sought his help or advice—advice given after careful consideration. A cricketer and a swimmer in his younger days, he took up golf in later years and enjoyed his holiday in North Berwick; he became an able player, as many of his friends found. To those who knew him he was a true friend.

F. J. Wilson.

SAMUEL FELIX DUFTON.

1867—1943.

Samuel Felix Dufton was born at Leeds on February 14th, 1867, the son of John Dufton of Bradford. He and his brother Arthur were educated at Bradford Grammar School, noted for the number of its scholars who attained distinction in after life. Of Dufton's contemporaries, one may mention Sir A. Colefax, K.C., Sir F. Dyson (Astronomer Royal), J. S. Fairbairn (gynæcologist), J. A. Gardner, W. W. Marriner (ship-builder), R. S. Morrell, G. A. Schott (mathematical physicist), and Cutcliff Hyne (originator of Captain Kettle), who is known to an even wider public.

Mr. Gardner has helped me with the foregoing list and given me a very interesting account of the Grammar School in the '80s. If space allowed, I should like to reproduce most of his letter but must limit myself to one or two quotations which give some idea of Dufton's youthful environment.

"We had the advantage of a really great Headmaster—the Rev. W. H. Keeling (Wadham, Oxford), who guided the school with great ability and acumen in the days when problems of education were urgent in the West Riding." Science was in charge of R. E. Steel (Magdalen, Oxford), who "kept his eye on individual boys, whom he used to persuade to come into his Science VI—either directly or through their parents. In this way he got together a more or less picked class—much to the indignation of masters of other subjects." Steel was evidently a good friend as well as a good teacher; Mr. Gardner speaks of him very warmly.

Dufton went to Trinity College, Cambridge, in 1885 as an Entrance Exhibitioner; he became a Sizar in 1886, a Scholar in 1888 and a Fellow in 1892. He took the Natural Sciences Tripos, Part I, in 1887 (1st Class) and Part II in 1889 (1st Class, Chemistry). Meanwhile he had taken the examinations for a London degree, gaining First Class Honours at the Inter. Sci. and Final B.Sc. Examinations. He headed the list in

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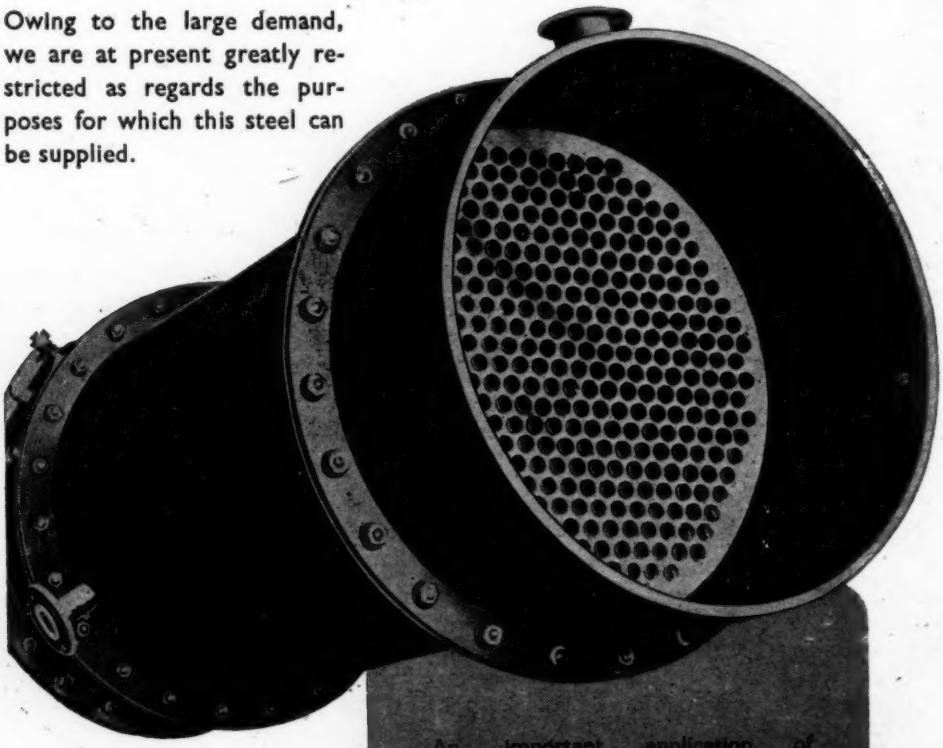

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